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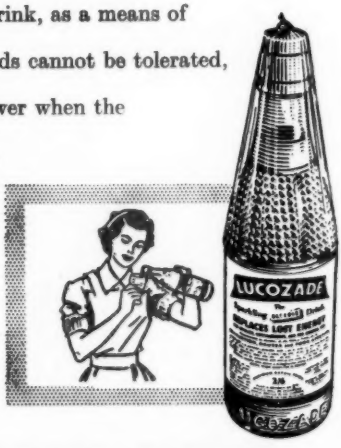

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Section of Physical Medicine

President—DORIS BAKER, M.D., F.R.C.P.

[*January* 12, 1955]

DISCUSSION ON HYDROCORTISONE

Dr. Hugh Burt (Director, Dept. of Physical Medicine, University College Hospital, London):

In this discussion we shall deal only with the effects of local injection of hydrocortisone into and around the joint; we shall make no reference to the effects of hydrocortisone given orally because (1) we have no personal experience with this method of administration, and (2) it may be assumed that its systemic antirheumatic effect is similar to that of cortisone.

Hydrocortisone

Hydrocortisone (17-hydroxycorticosterone) was isolated from the adrenal glands by Kendall in 1936, and also by Reichstein in the same year. It was not available in quantity until the end of 1950, by which time it was being synthesized by the firm of Merck & Co.

It is probable that hydrocortisone is a more important adrenal steroid than cortisone. This view is held by a number of different workers as the result of their investigations. Mason (1950) found that after injection of ACTH into 5 patients with rheumatoid arthritis hydrocortisone, *but not cortisone*, was recovered from the urine of 4 of them. Pincus, Hechter and Zaffaroni (1951) found that when they perfused isolated suprarenal glands with blood containing ACTH the amount of hydrocortisone isolated from the suprarenal veins was between ten and thirty times as great as the amount of cortisone.

The greater efficacy of hydrocortisone as compared with cortisone when given by local injection, which will be discussed later, is probably further evidence that hydrocortisone is the more important antirheumatic steroid of the two.

Action of Adrenal Steroids on Joint Disease

If sufficient doses of ACTH by intramuscular injection or of cortisone (intramuscularly or by mouth) are given to patients with rheumatoid arthritis, significant changes take place in the affected joints within a few days. The joint temperature decreases (Hollander *et al.*, 1951), and in the synovial fluid the cell count falls (due almost entirely to a decrease in the number of polymorphonuclear leucocytes), the viscosity rises, and the quality of the mucin improves (Duff *et al.*, 1951).

Identical effects are produced by repeated daily intra-articular injections of cortisone, or single doses of hydrocortisone.

These results support the hypothesis that adrenocortical steroids exert their favourable effect on the joints of rheumatoid arthritis at the connective-tissue level. If this is so, then, apart from the intrinsic disadvantages of repeated intra-articular injections, the injection of hormones into joints for their local anti-inflammatory effect is a logical procedure.

Freyberg was the first to inject a steroid intra-articularly (Freyberg *et al.*, 1951). He used cortisone and noted *in some cases* a favourable local response. In other cases, however, the joint became worse after the injection. This has been the experience of most who have injected cortisone into joints, and as at best its effects are short-lived it has been abandoned as a therapeutic procedure.

Hollander and his colleagues in Philadelphia first used hydrocortisone on a large scale for intra-articular injections in January 1951 (Hollander *et al.*, 1951). Since 1952 these workers have published numerous reports on hundreds of patients who have received many thousands of intra-articular injections of hydrocortisone. Their results appear to have been strikingly good. I have consulted these papers by Hollander and his colleagues a great deal in the preparation of this lecture.

Difference between Intra-articular Cortisone and Hydrocortisone

An interesting study was carried out in New York in 1952 by Ziff and his colleagues (Ziff *et al.*, 1952). Its objects were: (1) to investigate the effect of intra-articular cortisone and hydrocortisone, and (2) to compare the effects of the two compounds one with the other and with a series of control saline injections. They investigated 10 patients with arthritis of the knee (7 with bilateral effusions). First they noted any subjective improvement. Secondly they made objective records of changes in joint circumference, alterations in the inflammatory signs (redness and heat), and changes in mobility. Lastly they investigated

the synovial fluid, noting changes in viscosity, alterations in the cell count, and variations in the amino-tripeptidase concentration in the fluid. Amino-tripeptidase is an enzyme produced by breaking-down leucocytes and is, the authors believe, a reliable index of the degree of inflammation in the joint. The results in these 10 patients were as follows:

None of the 22 injections of the control substance (saline) produced any objective improvement, though after 3 (14%) of them there were significant changes in the synovial fluid.

With cortisone 4 out of 13 injections (31%) produced clinical improvement, but only 3 (23%) produced improvement in the synovial fluid.

On the other hand, of the 20 hydrocortisone injections 16 (80%) were followed by significant objective improvement, and 19 (95%) by significant changes towards normal in the properties of the synovial fluid.

As a result of this investigation Ziff and his colleagues concluded: (1) that the distinct superiority of intra-articular hydrocortisone over cortisone suggests that hydrocortisone or a metabolic derivative of it may be the active substance which induces the suppression of tissue reaction; (2) that cortisone given systemically is reduced either to hydrocortisone or to another active steroid; and (3) that the lack of significant local action on the part of cortisone, in the doses used, suggests that this reduction to a biologically active metabolite does not occur to a significant extent in synovial tissue.

Hollander puts forward another explanation—namely, that the difference between the two hormones lies in the fact that hydrocortisone is seven times less soluble than cortisone in blood plasma, and therefore, presumably, in synovial fluid. In other words, the cells of the synovial membrane can take up and retain hydrocortisone much longer than they retain cortisone.

Results with Intra-articular Hydrocortisone

It was not until March 1954 that hydrocortisone became available to us at University College Hospital. Our experiences with this substance are, therefore, necessarily limited. In view of this I think it best to discuss the results obtained by the American observers before describing our own.

Rheumatoid arthritis.—Hollander in the eighteen months between January 1951 and June 1952 gave 2,325 injections to 249 patients with rheumatoid arthritis (Hollander, 1953). All but 133 (5·7%) injections were considered successful, his definition of a successful injection being one that produced unequivocal improvement in symptoms and signs which lasted a minimum of three days. His most striking successes were in the knee-joint, where of 1,758 injections there were only 43 (2·4%) failures. The highest proportions of failures were in the temporo-mandibular and wrist joints (60% and 32% respectively).

The results obtained in the Department of Physical Medicine at University College Hospital in a very much smaller series of cases correspond closely to those of Hollander, as Table I (compiled by Dr. W. D. Fletcher) shows.

TABLE I.—RESULTS AFTER ONE WEEK OF 72 INTRA-ARTICULAR INJECTIONS IN 17 PATIENTS WITH RHEUMATOID ARTHRITIS

	Grade 1	Grade 2	Grade 3	Total
Knees	2	27	0	29
Elbows	0	16	3	19
Wrists	1	0	0	1
Interphalangeal joints ..	4	11	0	15
Shoulder	1	0	0	1
Hip	0	0	1	1
Bursæ, ganglia, tendon sheaths	3	2	1	6
Total	11	56	5	72

The results are assessed according to three grades; Grade 1 denoting complete relief of symptoms one week after injection; Grade 2 definite symptomatic relief justifying maintenance injections; Grade 3 no or only slight symptomatic relief, not justifying the risk of repeated injections.

Of the 72 injections performed on patients with rheumatoid arthritis, 11 produced complete symptomatic relief and 56 definite symptomatic relief; only 5 injections were considered failures. It should be noted that the knees were aspirated as completely as possible before each injection. Several observers, among them Freyberg (1952), have noted that the success of the injection varies according to whether or not the joint has been completely aspirated. One wonders, therefore, whether some of the benefit after hydrocortisone is in fact due to the aspiration.

A small but interesting group of cases were those classified under the heading "Bursæ, ganglia, tendon sheaths"; in 5 out of 6 instances hydrocortisone injection was markedly or completely successful.

Osteoarthritis.—In Hollander's series of patients with osteoarthritis treated by hydrocortisone there were only 13% failures in a series of 1,211 injections, the most favourable results being obtained in the knee-joint (90% success in over 1,000 injections); the highest proportion of failures was in the hip (53% in 77 injections).

Our own experience at U.C.H. has been limited to a few patients with osteoarthritis of the small joints of the hands and feet. The results in 3 patients were as follows:

(1) Carpo-metacarpal joint of thumb: 3 injections resulted in complete relief of symptoms for many weeks; 2 injections gave considerable relief.

(2) Interphalangeal joint of ring finger: 1 injection was followed by considerable symtomatic improvement which lasted for six months.

(3) Metatarso-phalangeal joint of big toe: 1 injection was followed by complete relief of symptoms.

Though this series is admittedly small, it suggests that treatment of osteoarthritis of the small joints of the hands and feet with hydrocortisone should be further studied, particularly as arthritis of these joints is notoriously resistant to other forms of therapy.

Extra-articular Sources of Pain in Arthritis of the Knee

There is one more group of cases that I wish to discuss briefly. Often in rheumatoid arthritis of the knee much of the pain arises from extra-articular structures. Not infrequently this pain can be controlled by procaine injections repeated at approximately fortnightly intervals.

A combination of hydrocortisone and procaine has in my experience had two results:

(1) Greater relief of pain resulted than when procaine alone was used.

(2) The period of relief has been doubled or trebled (lasting in some cases up to six weeks).

Conclusions

(1) In rheumatoid arthritis intra-articular hydrocortisone has been shown to have a striking local anti-inflammatory effect in a large proportion of cases. This effect, however, is of short duration, and the question arises whether the benefit obtained justifies the trauma and other possible complications of repeated joint injection in a disease which may well remain active for years.

(2) The indications for the use of hydrocortisone in rheumatoid arthritis at the present time seem to be as follows:

(*a*) Where only one or two peripheral joints are severely involved, and particularly where this localized disease is seriously interfering with the patient's activities.

(*b*) In cases where general systemic remedies such as gold, cortisone, or phenylbutazone (Butazolidin) are contraindicated.

(*c*) As an aid to physical methods of treatment where suppression of the inflammatory reaction in some cases appears to hasten the effects of manipulation, splinting, &c.

(3) In osteoarthritis of the easily accessible peripheral joints the local use of hydrocortisone seems to be justified, as the effects, if produced at all, are often long-lasting. Hydrocortisone seems to be particularly indicated for certain joints which are notoriously resistant to other forms of treatment, such as the carpo-metacarpal and the metacarpo-phalangeal joints of the thumb and the metatarso-phalangeal joint of the big toe.

(4) Hydrocortisone appears to enhance the effect of procaine injection in those cases of arthritis of the knee in which much of the pain arises from extra-articular structures.

(5) Finally, it must be fully realized that hydrocortisone is still under trial, and in systemic diseases such as the collagenoses it can never replace general medical treatment.

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Dr. Donald Wilson: I would like to point out that I am not reporting the results of a clinical trial. Authors have reported clinical trials of this preparation planned on different lines and if I had been reporting a clinical trial I would have planned these injections in a different way. The object of the use of hydrocortisone in these patients was to relieve pain and improve the range of movement of the affected joint. If other observations were made during the injections and as a result of the injections, these are isolated observations and any deductions that can be made should only be regarded as a pointer to the way rather than the way itself. In the cases quoted, most have had their articular disability for a long time since I did not regard hydrocortisone as the drug of choice in the early stages of either rheumatoid or osteoarthritis. In rheumatoid arthritis remission of the disease may be produced by several forms of systemic treatment and by local physical treatment. Only when the joint has failed to respond to the general and local treatment has hydrocortisone been considered. In osteoarthritis the same approach has been used. In the cases quoted, physical treatment of the affected joints has been given and continued during the injections of hydrocortisone. Hydrocortisone was given when the joint had failed to respond to other methods of treatment.

In spite of my cautious approach to the need for hydrocortisone in these cases—this caution being engendered by the belief that activation of a tuberculous joint, production of a pyogenic arthritis and perforation of a peptic ulcer may be more serious than the disability at present existing—I have given the great majority of these injections to Out-patients. I have used a facial mask if "colds" have been prevalent but I have not used gloves; the skin of the patient has been cleaned by spirit and I have taken care to dry the skin by means of sterile gauze after the application of spirit. The syringes and needles are autoclaved. I mention these points because in the U.S.A. there has been controversy on this subject, some authors advocating strongly that intra-articular injection is dangerous without full operating theatre sterility and others maintain that simple but adequate sterility such as can be found in Out-patients is enough. Hollander is of the latter school and if one can give and supervise over 7,000 intra-articular injections with a very small morbidity rate, then that opinion is worth consideration. In the past eighteen months I have given over 250 injections of hydrocortisone into the knee-joints and the region of the hips To the best of my knowledge there have been only 3 untoward occurrences. In one case two weeks after the injection, the patient was pushed down in a scramble for a late 'bus and he sustained a hæmarthrosis. A woman who had received an injection for osteoarthritis of the knee with a large effusion was walking briskly, slipped and fell—a hæmarthrosis resulted. In a third patient, again with osteoarthritis, following the injection there was complete relief of pain and full range of movement, but at the end of four days he impacted a loose body in the affected joint.

I was tempted to compare the results of injection with hydrocortisone with those of procaine. This task I found too difficult although the procaine injections had been done in the recent past and details were available but the conditions under which the injections were given were different; the criteria of improvement were the same and clinical details were not missing but I felt that the individual assessment was probably different. For these reasons I felt that the comparison would be unfair.

The improvement in the range of movement was estimated by measurement when the patient was non-weight bearing. An improvement of 0–5 degrees can be regarded as showing in reality no improvement. 5–20 degrees can be regarded as definite improvement. Full range of movement implies that the patient was able to put the affected joint through the full range of movement when non-weight bearing. In certain cases the limitation of movement before injection might be slightly less than 10 degrees. The assessment of pain was made on weight bearing: the ability of the patient to take the body weight on the affected leg.

TABLE I.—RHEUMATOID ARTHRITIS OF KNEES

Number of knees injected 44		
Range of movement improved by		
0–5 degrees	5–20 degrees	Full
8	12	24
PAIN		
No improvement	Improvement	Free from pain
7	19	18

Table I shows the bare results of 76 injections of hydrocortisone into 44 knee-joints. In 24 cases full range of movement was obtained and in 18 cases complete freedom from pain.

TABLE II.—RHEUMATOID ARTHRITIS OF THE HIPS

Number injected 11

Range of movement improved by

0–5 degrees	5–20 degrees	Full
3	6	2

PAIN

No improvement	Improvement	Free from pain
2	7	2

Only 11 hip-joints were injected (Table II). Only 2 showed full range of movement at the end of two months and in only two cases complete freedom from pain obtained.

These results contrast with the relatively good results with injection into the knee-joint. I think, in common with others, that the ease of injection into a knee compared with a hip is the principal cause for the disparity in the results.

TABLE III.—OSTEOARTHRITIS OF KNEES

Number of injections 23
Number of knees injected .. 14

Range of movement improved by

0–5 degrees	5–20 degrees	Full range of movement
	6	8

In all the 14 cases injected there was a significant improvement in the range of movement (Table III).

TABLE IV.—OSTEOARTHRITIS OF HIPS

Number injected 17

Range of movement improved by

0–5 degrees	5–20 degrees	Full
8	6	3

PAIN

No improvement	Improvement	Free from pain
3	13	1

As in rheumatoid arthritis of the hips the results (Table IV) are less favourable than with a similar condition of the knee-joint.

From these Tables I gained the impression that hydrocortisone is of some value in correcting deformity in joints and procuring relief of pain. Results are more easily assessed in the knee-joint and the injection should be undertaken early in the disability before contraction has taken place in the muscles around the joint. I cannot be certain that a satisfactory result will be obtained at any particular phase. I have seen more than once a poor response to an intra-articular injection of a knee-joint yet an excellent result to an injection of a hip-joint in the same patient.

It is too early to estimate the duration of the results of an intra-articular injection of hydrocortisone. One injection of hydrocortisone may produce improved range of movement from one to six months and even longer.

For what period should the injections of hydrocortisone be given intra-articularly? It is probable that their main use is in the prevention and assistance of correction in articular deformities and when these results have been achieved then hydrocortisone should be discontinued. Although hydrocortisone has been of value in the alleviation of pain it may be that its real value is in the early stages of an exacerbation of the arthritic disorder when, combined with rest, a dramatic and longstanding relief may be obtained.

Dr. C. E. Quin (Arthur Stanley Institute, Middlesex Hospital, London):

I shall briefly mention the results of local hydrocortisone injection in soft tissue lesions.

Tennis Elbow

Holander (1953*a*) referred to the successful treatment of tennis elbow in his summary of two years' experience in the use of hydrocortisone locally. Cyriax and Troisier (1953) also reported favourably on this treatment. Murley (1954) treated 19 patients with hydrocortisone and 18 control patients with procaine. After one week the results in the hydrocortisone-treated patients were 14 improved, and after one month, 2 improved and 14 improved greatly.

The figures for the control cases were: at one week, 7 improved, and at one month, 7 improved and 2 improved greatly. Murley concluded that local injection of hydrocortisone causes relief of symptoms in a high proportion of cases of tennis elbow. He added "relapse is common, but this usually responds to a second injection". This has been our experience at the Middlesex Hospital, and Dr. F. A. Binks and I reported relief of symptoms in 27 out of 31 patients, the injection being considered successful if relief of symptoms resulted for at least one week (Quin and Binks, 1954). Freeland and Gribble (1954), treated 7 patients with hydrocortisone and 7 with procaine and found no difference in the results. Both procaine and hydrocortisone produced distinct improvement in half the cases, lasting two to four months. This is certainly a better result than is usually obtained with procaine for the benefit lasts, as a rule, no longer than the duration of the local anæsthesia.

At the Middlesex Hospital we now have a series of 57 cases of tennis elbow treated with hydrocortisone. The duration of symptoms was under two months in 20 patients and under six months in 47 of the 57 patients. The results of treatment assessed at one to three weeks after the injection were as follows: 45 had complete relief or almost complete relief. By almost complete relief I mean they had no symptoms in ordinary everyday activities though aching might occur after heavy work. A reduction in severity of symptoms was claimed by 8 patients and in 4 patients there was no benefit. Relief was obtained with one injection in 41 of the 45 patients who had complete or almost complete relief, but the other 4 required a second injection. Several injections were tried in those experiencing partial relief but without further benefit.

The method of giving the injection is simple. Probably all that is necessary is to inject the hydrocortisone into the most tender area in the region of the lateral epicondyle. I inject procaine first and then ask the patient to grip and to extend the wrist against resistance. There should be no pain when tested in this way, thus supporting the diagnosis of a local soft tissue lesion.

When observed a week after injection, there is no pain on gripping or extension of the wrist in successful cases, though very slight tenderness of the lateral epicondyle may persist. The dose of hydrocortisone we have used for most patients is 25 mg. This may well be more than is necessary, as we have had successful results with half this amount in 10 cases.

I have given the results of treatment in 57 cases at periods varying from one to three weeks after the injection. To judge the value of hydrocortisone in this condition it is necessary to know more about the duration of benefit from the injection and about the number which relapse. The original series of 31 patients (Quin and Binks, 1954) have, therefore, been followed up. Of this 31, we have had no recent news of 4. Of the remaining 27, 8 have maintained the relief of symptoms following one injection, the period of observation being eight to ten months. 6 patients have relapsed once but have been relieved by a second injection. They have had relief for periods of seven to nine months, with two injections. 2 patients have relapsed twice but relief has been maintained by further injections for seven to nine months. Thus 16 out of 27 patients have had relief of symptoms with one or more injections for periods of between seven to ten months to date.

Of the remaining 15 in the group of 31 patients, 2 relapsed at four months and one at six months, but the symptoms were not so severe as they were originally. Incidentally, it is usually though not always the case that the symptoms on relapse are not so severe as the original symptoms. In 2 further patients there was a return of symptoms at six weeks and two months but they were so mild that a further injection was considered unnecessary. In 3 patients there was a full return of symptoms at ten days, two and a half months and three months, but the patients did not favour a second injection.

Of those for whom follow-up is incomplete, 1 is known to have had relief for six months, relapse then occurred but the duration of relief from a second injection is not known. The other 3 patients for whom follow-up is incomplete are known to have been relieved for three to four weeks, but we have not seen or heard from them since.

There were 3 absolute failures in this series of 31 cases.

To summarize the results in 31 cases. 17 are known to have relapsed. Relapses occurred at periods varying from ten days to six months, but most relapses occurred between two and four months. It has been possible to give relief, which is still maintained, to 16 out of 27 patients for periods varying from seven to ten months with one or more injections.

5 cases of medial epicondylalgia or golfer's elbow have been treated with hydrocortisone. 4 experienced complete relief and 1 partial relief following the injection. 3 of these patients relapsed.

Subacromial Bursitis and Supraspinatus Tendinitis

Hollander (1953*b*) stated that hydrocortisone injections were successful in relieving symptoms in 80% of cases of acute subacromial bursitis but that symptoms were relieved in only 49% of cases of chronic subacromial bursitis. Ramsey and Key (1953) state that of

12 patients with acute calcific bursitis, 10 were completely and 2 partially relieved with one or two hydrocortisone injections, and they considered the response better than to any other form of treatment. In 15 patients with chronic bursitis—the frozen shoulder group—only 2 were completely relieved, 6 partially relieved and 7 had no benefit. They suggest that the reason for failure in the chronic cases is that the bursa is partially obliterated.

We have treated 18 cases of painful shoulder due to subacromial bursitis or supraspinatus tendinitis. 4 of these were cases of acute bursitis. The acute cases had severe pain at rest, preventing sleep, and the pain was greatly increased by the slightest movement. 37·5 mg. hydrocortisone was injected into the bursa in these cases. In 3 cases the severe rest pain was relieved within forty-eight hours, but there was still pain on movement, though not of the former severity. In one patient marked relief occurred but there was still some pain at rest. Improvement then continued and there was full, painless movement in one patient at one month, in another at six weeks, but in a third full movement was not achieved for six months. The fourth patient is still improving one month after injection.

We have treated 14 cases of painful shoulder in which the symptoms were not acute. 9 patients had had symptoms for three to six months, 4 for two months or less and 1 for a year. Marked relief of symptoms occurred in 7 patients and no benefit in 7. 7 patients had marked restriction of movement and only 2 of these improved. 7 had full movement or limitation of rotation only and of these 5 improved and 2 had no benefit. Those who improved had had their symptoms for an average of three months, whereas those with no benefit had had them for an average of five months.

It seems that success is most likely to be achieved in acute cases and in those without severe limitation of movement. Ramsey and Key (1953) consider that the treatment of chronic cases with marked limitation of movement, that is frozen shoulder, is manipulation combined with a hydrocortisone injection, the latter making the post-operative course less painful and cure more prompt and certain.

We have also injected the subacromial bursa with hydrocortisone in 12 patients with rheumatoid arthritis in whom there was severe shoulder pain considered to be due to bursitis. Fluid was obtained from the bursa in 4 cases. Following the injection 8 patients experienced marked relief of pain, this being accompanied by some increase in shoulder movement in 7. In 1 patient there was only slight improvement and in 3 no benefit. One patient has not relapsed during one year of observation, but relapse has occurred in the other 7 after intervals varying from three to eight weeks. It can be concluded that injection of the bursa is a worthwhile procedure in subacromial bursitis due to rheumatoid arthritis and that it may help the patient over an acutely painful episode.

Other Bursæ

I have only treated one case of traumatic prepatellar bursitis. There was relief of pain and no recurrence of fluid when she was seen three weeks after the injection, but later follow-up reveals that the pain gradually returned a few weeks after she was last seen. Henderson and Henderson (1953) refer to 10 cases of prepatellar bursitis and 4 cases of olecranon bursitis of traumatic origin, which were successfully treated with hydrocortisone. Only one case relapsed in a period of four months' observation. Incidentally they considered that 12·5 mg. hydrocortisone was as effective as a larger dose in the treatment of these forms of bursitis.

I have only treated 2 cases of semimembranous bursitis complicating rheumatoid arthritis. In one the bursa disappeared after two injections and in the other there was no benefit.

Plantar Fasciitis

We have treated 4 cases. In 3 patients there has been almost complete relief of symptoms. 2 of these patients required a second injection to produce a beneficial result. There has been no recurrence during four months' observation in 2; 1 successful case was only done a month ago. The fourth patient had no benefit from two injections.

Pain near the Greater Trochanter

I would like to mention another small group of cases. 6 patients have complained of pain in the region of the greater trochanter. Examination revealed no clinical or radiological evidence of arthritis of the hip, but in each case there was an acutely tender area in the region of the greater trochanter. The symptoms had been present for periods of a few months to five years. In 1 patient the X-ray showed small opaque spots presumably due to calcification in the region of the greater trochanter. 5 of these patients had marked relief from a hydrocortisone injection into the tender area and in 2 it was complete. One had only moderate relief. In 2 patients relief had been maintained for over four months without relapse. One patient relapsed at four months but responded to a second injection. The other 2 have not been observed for long.

We have injected tender areas near the ankle-joint which were thought to be responsible for symptoms with success in 3 cases and failure in 4.

Tenosynovitis

We have injected very few cases of tenosynovitis. I can record success in 1 case of tenosynovitis associated with rheumatoid arthritis and 1 case of de Quervain's tenosynovitis. I have also had 1 failure in de Quervain's tenosynovitis.

Howard *et al.* (1953) record success from local injection of hydrocortisone in all of 8 cases of tenosynovitis, 6 cases of trigger finger and 2 cases of de Quervain's tenosynovitis. It is of interest that no improvement resulted from hydrocortisone injection in 5 cases of simple ganglion in their series.

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Reiter's Disease: A Review of the Present Position

By J. F. BUCHAN, M.A., M.D., M.R.C.P.

REITER'S disease has been the subject of considerable interest during recent years and many articles about it have appeared in the medical press. In spite of this, it remains a very ill-defined syndrome and some doubt that it exists at all. Others, though recognizing its existence, hold widely differing views as to its definition, ætiology and mode of transmission. The assumption that Reiter's is a venereal disease, for instance, would be disputed by most continental writers, who regard it as a complication of bacillary dysentery.

The disease has been given many names (Table I), none of which is entirely satisfactory,

TABLE I.—REITER'S DISEASE—SYNONYMS

Rheumatismus intestinalis cum ulcere (Caelius Aurelianus).
Arthritis dysenterica (Huette, 1869).
Arthritis enterica (Schittenhelm and Schlecht, 1918).
Ruhrrheumatismus (Dorendorf, 1917).
Ruhrrheumatoid (Schemensky, 1918).
Arthritis urethritica (Moltke, 1936).
Syndrome conjonctivo-uretro-synovial (Fiessinger and Leroy, 1916).
Reiter's disease (Musger, 1934).
Spirochætosis arthritica (Reiter, 1916).
Infectious uro-arthritis (Hollander, 1953).
Venereal arthritis (Ford, 1953).
Dysenteric arthritis (Harkness, 1949).
Non-gonococcal arthritis (Harkness, 1949).

and in this article it will be referred to as Reiter's disease or syndrome as it is thus most widely known.

The syndrome may be defined as one of unknown ætiology, characterized by the presence of three essential symptoms, urethritis, conjunctivitis and arthritis.

The case described by Reiter (1916) showed the characteristic triad of symptoms and followed an attack of diarrhœa and abdominal pain. Similar cases complicating dysentery had, however, been reported before. Indeed, Manson-Bahr (1943) states that Caelius Aurelianus mentioned post-dysenteric arthritis in the fifth century; certainly Kuster

described arthritis and conjunctivitis as a dysenteric complication in 1871 and Markwald similarly reported a case developing the complete syndrome in 1904.

Reiter's syndrome appears most often after Shiga or Flexner dysentery but cases have been reported after amœbic dysentery, *Giardia lamblia* infection and after simple diarrhœa. The incidence of arthritic complications following dysentery varies greatly. Manson-Bahr mentions two epidemics of bacillary dysentery in the Fiji Islands, one in 1897 in which 10% of cases developed this complication and another thirteen years later in which there were none. In Paronen's (1948) big series of cases, seen during a Flexner outbreak in Finland during the late war, only 0·2% developed Reiter's disease. 34 or 10% of these cases occurred in women. Another interesting point made by Paronen was that there was no correlation between its incidence and the severity of the diarrhœa.

This post-dysenteric type of case has not so far been reported in people dwelling in this country. Harkness (1949), who has reported the largest British series so far, states that true Reiter's disease is one in which the primary focus of infection is an abacterial urethritis of venereal origin. This venereal type of Reiter's disease occurs almost exclusively in males. It has recently been observed that the usual form of rheumatism following gonorrhœa is clinically identical to that following abacterial urethritis (Ford, 1953); moreover neither is affected by penicillin, and the gonococcus, it must be remembered, is extremely sensitive to penicillin. For these reasons it is believed that the usual form of rheumatism following gonorrhœa is identical to that following abacterial urethritis. This clinical entity, which we refer to as Reiter's syndrome, has a recognizable distribution and clinical course. The term gonococcal rheumatism should be reserved for those cases in which the *Neisseria gonorrhœæ* is recovered from the affected joints and tissues. Table II summarizes our present knowledge of these precursory infections.

TABLE II.—REITER'S DISEASE—PRECURSORY INFECTIONS

(1) Intestinal. Bacillary or amœbic dysentery. Diarrhœa. (Both sexes affected).

(2) Urethral. Non-specific urethritis. Gonorrhœal urethritis. (Males only affected).

CLINICAL PICTURE

The initial symptom varies in the two types. The venereal cases present first with either gonococcal or abacterial urethritis and this is followed by conjunctivitis and arthritis in that sequence. In the post-dysenteric cases there is no set order in the development of the triad (Table III).

TABLE III.—REITER'S DISEASE—INITIAL SYMPTOM IN POST-DYSENTERIC CASES (Paronen, 1948)

(1) Monosymptomatic, 69%

urethritis	23·9%
arthritis	23·3%
conjunctivitis ..	21·9%

(2) Bisymptomatic in less than 25% of cases, usually conjunctivitis and urethritis, sometimes conjunctivitis and arthritis, seldom urethritis and arthritis simultaneously.

(3) Less than 8% of cases showed the entire triad at onset.

The urethritis may be acute or subacute and the urethral discharge may be of very short duration or may last several days.

The inflammation of the conjunctivæ is commonly bilateral and also varies greatly in severity. Sometimes it is mild and fleeting but often it is severe and profusely purulent. It is accompanied by local pain, lacrimation and photophobia. Recurrent attacks are common.

Generally the articular component dominates the clinical picture. The onset of the arthritis is accompanied by malaise, fever and a raised erythrocyte sedimentation rate. A strong characteristic is a predilection for the condition to affect the knees, ankles and feet. Knee-joint effusions are common. Circumscribed areas of tenderness over the periosteum in the region of the heels and knees are a feature of many cases and localized swelling and tenderness of one part of the periarticular structures in the absence of generalized swelling of the whole joint is typical. These localized areas of inflammation have been variously ascribed to periostitis, tendinitis, myositis or bursitis.

The frequency with which the various joints are involved is shown in Table IV.

TABLE IV.—REITER'S DISEASE—FREQUENCY OF JOINT INVOLVEMENT

URETHRITIS CASES (Harkness, 1949)		DYSENTERIC CASES (Paronen, 1948)	
Joint	%	Joint	%
Knee	70·3	Knee	25·4
Ankle	55·4	Ankle	16·2
Small joints of feet	25·0	Toes	8·0
Small joints of hands	18·6	Shoulder	7·8
Mid-tarsal	10·0	Wrist	6·5
Wrist	9·2	Fingers	6·5
Periostitis	8·0	Metatarsal	6·2
Sacro-iliac	5·4	Sacrum	6·0
Shoulder	4·6	Elbow	4·9
Elbow	3·8	Hip	4·2
Sterno-cl.	0·6	Vertebral (L. and Th.)	2·8
Acromio-cl.	0·6	Vertebral (C.)	1·5
Intervertebral	0·4	Metacarpal	1·4
		Others	2·6

It will be seen how strikingly similar this is in the two types of case.

A feature of this arthritis is the occurrence of multiple attacks without the development, elsewhere than in the feet, of residual joint damage. Chief among the permanent deformities that do occur are calcaneal spurs, pes cavus or planus and dorsiflexion and fibular deviation of the toes at the metatarso-phalangeal joints. The joints of the upper limbs and of the vertebral column are much less frequently involved. Ulnar deviation of the fingers is not seen.

The main clinical features of Reiter's arthritis are summarized in Table V.

TABLE V.—REITER'S ARTHRITIS—CLINICAL FEATURES

Fever, malaise, raised E.S.R.
Joints of lower limbs predominantly affected.
Effusions common.
Circumscribed areas of tenderness over periosteum.
Localized swelling and tenderness of one part of peri-articular structures in the absence of generalized swelling of the whole joint.
Multiple attacks without the development of residual joint damage except in the feet.

The duration of the arthritis varies greatly. It may persist for only a few days and be represented by a short-lived arthralgia affecting principally the joints of the lower limbs, or it may last for as long as three years. In the majority of cases the duration is two to four months. Spontaneous and complete recovery occurs in 80% of cases but unfortunately relapses are frequent.

The syndrome may present in a complete or incomplete form and it is when it is incomplete that difficulties in diagnosis arise.

The condition has to be differentiated from true gonorrhœal and dysenteric arthritis. In both of these the causative micro-organism can be obtained from the fluid in the affected joints. Reiter's arthritis may also be confused with rheumatoid arthritis but Ford, after following up a number of cases over a long period, found no tendency in them to develop typical rheumatoid joint deformities. The two can be distinguished on clinical grounds.

Stevens-Johnson's syndrome, Behcet's syndrome, arthropathic psoriasis, acute rheumatic fever, palindromic rheumatism and intermittent hydrarthrosis also enter into the differential diagnosis.

LABORATORY AND RADIOLOGICAL FINDINGS

The laboratory and X-ray findings are non-specific and do not help much in making the diagnosis.

The urethral discharge is either abacterial or gonococcal, the joint effusions are sterile and the swabs taken from the conjunctivæ do not show the presence of pathogenic organisms.

Storm-Mathisen (1946) has described a skin test in which he employed diluted joint exudate and lymphatic gland emulsion obtained from a typical case. In a preliminary report he had five positive readings in cases of Reiter's disease and negative readings in controls.

Complications and Sequelæ

The frequency of relapse and the tendency for the development of chronic foot deformities have already been mentioned. Other complications are rather rare. However, penile skin lesions—the so-called balanitis circinata—develop in a high percentage of cases. Keratodermia blenorrhagicum requires special mention. It is a highly characteristic rash associated with Reiter's disease and is commoner than has been supposed. The development of ankylosing spondylitis in certain cases is an interesting observation. These and other complications are shown in Table VI.

Table VI.—Reiter's Disease—Complications

(1) Genito-urinary system:
Cystitis. Nephritis.
Prostatitis. Epididymitis. Orchitis.
(2) Ocular Lesions:
Iritis. Iridocyclitis. Corneal ulceration.
Keratitis. Optic neuritis.
(3) Locomotor System:
Bursitis. Tendinitis. Tenosynovitis.
(4) Skin Lesions:
Keratodermia blenorrhagicum.
Balanitis circinata 87%.
Eczema. Herpes labialis. Urticaria.
(5) Respiratory System:
Acute rhinitis at onset.
Dry pleurisy 10–20%.
(6) Cardiovascular System:
Myocarditis. Pericarditis.
Other complication include neuritis, sialadenitis, splenomegaly and enlarged lymphatic glands.

The prognosis as regards life is good—no fatalities from Reiter's disease have been reported.

Theories of Ætiology

The striking clinical similarity of the arthritis of the dysenteric, gonorrhœal and abacterial urethritis cases makes it appear likely that they may be all variants of one and the same disease and may be due to a single ætiological factor.

The cause of Reiter's disease is unknown but four main theories have been put forward.

(1) *The bacterial theory.*—Adherents to this theory believe that there is no such entity as Reiter's disease and that if a sufficiently protracted search is made this will always reveal the presence of the gonococcus or of a dysentery bacillus in the affected joints and tissues. All are thought to be due to a bacterial infection spreading from a primary focus in the urethra or in the bowel. However, joint effusions are invariably sterile in this syndrome and even maceration and culture of synovial tissue taken from a typical case failed to reveal the presence of any micro-organisms (Bauer and Engleman, 1942). Moreover, Reiter's disease is resistant to all antibiotics. Therefore, the theory of joint infection by a bacterium in its usual form must be rejected.

(2) *The allergic theory.*—This suggests that Reiter's disease may be a manifestation of allergy to bacterial products, rather on the lines of the relationship of the onset of rheumatic fever and the group A hæmolytic streptococcus.

While allergy is a possibility there is as yet no positive evidence to support it.

(3) *The rheumatoid theory.*—The idea of a post-gonococcal form of rheumatoid arthritis was first put forward by Hench in 1948. Since there are clear clinical differences between rheumatoid arthritis and the articular manifestations of Reiter's disease they are best regarded as two different diseases each due to a separate cause.

(4) *The separate infective agent theory.*—Supporters of this theory believe that Reiter's disease is a specific infection but so far the nature of this infection has not been elucidated.

Reiter himself believed that the condition was a spirochætal one and claimed to have cultured such an organism from the blood. He was, however, unable to repeat this in later cases and other workers have also failed to confirm his original finding.

The idea that Reiter's syndrome is a virus infection is a definite possibility. Harkness (1948) thought that he had detected inclusion bodies in scrapings from lesions and Dunham *et al.* (1947) have claimed to have isolated a virus which is capable of producing conjunctivitis in mice.

At the moment an infection by pleuropneumonia-like organisms is the theory that is most widely held. Certainly much evidence points in this direction. These organisms, which are generally regarded as variant growth-forms of ordinary bacteria, have been found by Dienes *et al.* (1948) in a large number of men suffering from abacterial urethritis. A high percentage of these patients were found to be suffering from acute arthritis and some of them from typical Reiter's disease. It is therefore likely that certain strains of these organisms have pathogenic activity in the male genito-urinary tract and may be ætiologically related to Reiter's disease.

Treatment

The value of any therapeutic measure in a self-limited disease is always difficult to estimate. However, in the treatment of Reiter's disease certain common-sense principles should be adhered to.

Bed rest is necessary usually in the articular stage of the illness for, in addition to malaise and fever, it is usually the weight-bearing joints that are affected.

Irrigation of the eyes and the urethra with some mild simple disinfectant solution is probably worth while.

Inflamed joints should be rested in padded plaster of Paris splints and all joints should be put through full range of possible movement daily while the patient is confined to bed.

Aspirin or codeine is useful in relieving pain. Penicillin will eliminate any concomitant gonococcal infection and sulphaguanidine may be required for the treatment of the bacillary dysentery.

Cortisone and ACTH produce only a temporary remission of symptoms.

Fever therapy and intramuscular gold injections are not recommended for the treatment of the arthritis.

Conclusion

Reiter's disease is probably a condition *sui generis* and is of unknown ætiology. It is characterized by the presence of three essential symptoms, urethritis, conjunctivitis and arthritis. It follows abacterial and gonococcal urethritis in men and dysentery in both sexes.

The articular component of the syndrome generally predominates and the condition has a typical picture and course. It is a self-limited condition, which is resistant to treatment. There is some evidence that it may be due to an infection by a strain of the pleuropneumonia group of organisms.

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Section of Surgery

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Injuries to the Recurrent Laryngeal Nerves During Thyroid Operations

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DURING the past six months, following a medico-legal case which was won by the hospital concerned, we have investigated the incidence of injury to the recurrent laryngeal nerves during operations on the thyroid gland. All cases submitted to operation were examined laryngologically both before and after operation.

These cases consisted mostly of nodular goitres with pressure symptoms or secondary thyrotoxicosis and a few cases of primary thyrotoxicosis (most of the latter cases being treated medically).

There were 4 cases of temporary weakness of 1 vocal cord after operation, of which there were 2 in which an abnormally placed nerve was identified during operation, 2 in which the nerves were identified and guaranteed to be intact at the end of operation. These cases were all symptomless apart from slight hoarseness and would not have been recognized apart from routine examination.

There are opposing views as to the best method of avoiding injury to the nerve. I follow Mr. C. A. Joll's technique of not dissecting out the nerve deliberately. It is usually possible to see or palpate it through the fascia, and the more dissection that is done in its vicinity, the more likelihood will there be of damaging it or its small branches by bleeding or fibrosis during healing.

I consider it is justifiable to state that there is an inherent risk to the nerves during operations on the thyroid gland.

The Surgery of the Recurrent Laryngeal Nerve

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MY part in this discussion is to summarize the results of an investigation into certain aspects of the anatomy of the recurrent laryngeal nerve, and to discuss their significance in the surgery of the thyroid gland. The observations which were made were correlated with those of previous authors and a detailed report is in the press (Bowden, 1955). The points which will be considered are the relevant parts of the deep cervical fascia, the relations, the frequency and site of branching of the recurrent laryngeal nerve, and certain vascular anomalies.

OBSERVATIONS

(1) *Fascia.*—In addition to the true capsule, the thyroid gland is invested with a distinct outer covering formed by the pretracheal fascia, the attachments and extensions of which are not generally recognized, although some were described by Sir James Berry in 1901. The pretracheal fascia, which has lateral extensions to the carotid sheath, covers the anterior aspect of the gland and on reaching its posterolateral border splits into two layers. One layer passes behind the whole posterior surface of the gland, meeting the layer from the other side, and this layer has conspicuous bilateral thickenings at and just above the level of the isthmus, attaching the gland to the trachea and the lower border of the cricoid cartilage. This condensation of connective tissue, which is even more marked when the gland is enlarged, was named the suspensory ligament by Berry in 1888, the adherent zone by Berlin (1950) and Armstrong and Hinton (1951), and the lateral ligament by Rundle (1951). The latter term will be used since it avoids any confusion with the levator glandulæ thyreoideæ.

The other, more posterior layer of pretracheal fascia, passes behind the œsophagus and is continued upwards on to the posterior wall of the pharynx, and is attached laterally to the prevertebral fascia, forming a well-defined retro-pharyngeal and retro-œsophageal space. The pretracheal fascia and its extensions thus form a compartment lateral to the trachea and œsophagus. The cross-sectional area and shape of this space vary according to the level in the neck. The recurrent laryngeal nerve and the terminal parts of the inferior thyroid arteries lie within the space embedded in lobules of fat which are elongated and tend to lie parallel to the course of the nerve.

(2) *Relations of the recurrent laryngeal nerves to the tracheo-œsophageal groove and lateral ligament.*—It is commonly stated that after looping round the aortic arch on the left, and the subclavian artery on the right, the recurrent laryngeal nerve ascends within the tracheo-œsophageal groove. However, only 73 out of 134 nerves on the right, and 85 out of 133 on the left, were in the groove and the rest were in an exposed position, anterior and sometimes well lateral to the groove. The differences between the two sides are not statistically significant.

Berry in 1888 stated that the recurrent laryngeal nerve lay in immediate contact with the posterior and outer surface of the lateral ligament, but in 47 out of 116 cases the right recurrent laryngeal nerve actually traversed the ligament, and on the left 40 out of 114 cases showed this same relationship.

The one constant relationship of the nerve or its laryngeal branches in the field of operation appears to be its point of entry into the larynx immediately behind the inferior cornu of the thyroid cartilage at or just above the lower border of the inferior constrictors of the pharynx.

(3) *Penetration of the thyroid gland by the recurrent laryngeal nerve.*—In the series of personal observations the recurrent laryngeal nerve was not found to penetrate the gland, although in one case the nerve was distorted by the presence of a small adenoma. Out of 1,991 cases the right nerve was found to penetrate the gland twenty-nine times and the left nine times. In an isolated instance the nerve was reported to penetrate the capsule alone. The appearance of penetration may be simulated when the nerve runs between the main body of the gland and an adenomatous outgrowth.

(4) *Relations of the recurrent laryngeal nerves to the inferior thyroid vessels.*—In all the personal observations the middle and inferior thyroid veins lay on a plane which was anterior to the nerve. The relationship of the nerve to the arteries varies considerably. Out of 1,650 cases there was an aberrant nerve in 4, an absent inferior thyroid artery in 3. Taking the left and right sides together the nerve lay posterior to the artery in the greater proportion of cases, and in the remainder there were equal chances of the nerve being either anterior to the artery or intermingled with its branches. Further analysis shows that an aberrant nerve is more common on the right, and on this side there are almost equal chances of finding the nerve anterior, posterior, or intermingled with branches of the artery. On the left-hand side the nerve is most likely to be posterior to the artery and least likely to be anterior. Since there is so much variation between the relationship of the vessels and nerves, it is of interest to note that symmetrical arrangements on right and left sides were found in 99 out of 311 cases. The precise relationships between branches of the nerve and artery are difficult to follow since the artery may be absent, may divide into two main branches well lateral to the gland, or may have as many as four to six terminal branches, whilst the nerve itself may be undivided as it enters into the larynx or it may have as many as six laryngeal branches. This gives a possibility of sixty different types of relationship, a number even greater than that found by Reed (1943). It is therefore impracticable to follow through this detailed arrangement, but it is important to note that in certain cases the intermingling of the nerve and vessels causes distortion of the nerve, sometimes in the undisturbed state and at others only when the gland is dislocated forward, even when the artery has been divided and is quite free at the lateral extremity.

(5) *Branching of the recurrent laryngeal nerves.*—The recurrent laryngeal nerve invariably gives branches to the trachea and the œsophagus and in addition there may be extra-laryngeal branches destined for the larynx itself. Symmetrical unbranched nerves were found to enter the larynx in 35 out of 126 subjects. Out of 1,174 cases 434 were found to have extra-laryngeal branches. Out of 300 nerves with such branches, 245 nerves broke up into two, 34 into three, 17 into four, 3 into five, and 1 into six branches. There are almost equal chances of the branching taking place in relation to the middle third of the gland or at or below the lower third. It is least likely to occur in relation to the upper third of the gland. The lowest point at which branching is reported to have taken place is 4 cm. below the inferior constrictor of the pharynx (Sunderland and Swaney, 1952).

(6) *The inferior thyroid artery.*—The inferior thyroid artery usually arises as a branch of the thyrocervical trunk. In 2 out of the 30 cases investigated personally the artery was

absent on the left side, and when this series was correlated with published cases, the artery was found to be absent in 7 out of 473 cases on the right and in 15 out of 469 cases on the left. In this same group of cases the thyroidea ima was found seven times, and in one reported by Armstrong and Hinton (1951) the left inferior thyroid artery arose from the common carotid artery. Rarely, the inferior thyroid artery may arise from the innominate artery, the transverse cervical, suprascapular, vertebral, internal mammary artery, or directly from the arch of the aorta or subclavian trunk. Through the courtesy of Professor E. W. Walls of the Middlesex Hospital it is possible to report a case in which the inferior thyroid artery arose directly from the subclavian artery, passed behind the vertebral artery and entered the gland anterior to the recurrent laryngeal nerve, which looped round the subclavian in the usual manner. The inferior thyroid artery may be double (Lambert Rogers, 1929), or an additional accessory inferior thyroid artery may arise from the common carotid (Poirier and Charpy, 1912). The primary division of the artery, which usually takes place just lateral to or behind the thyroid gland, may take place laterally, just medial to the carotid sheath, and there may be considerable variation in the calibre of the vessel.

(7) *Aberrant recurrent laryngeal nerve.*—An aberrant recurrent laryngeal nerve may be associated with the right subclavian artery which arises as a separate entity from the posterior aspect of the aortic arch, just distal to the origin of the left subclavian artery. 3 such cases have been noted in the Department of Anatomy at the Royal Free Hospital School of Medicine and the incidence was estimated as roughly 1 in 200 cases. The abnormality of the subclavian is thought to be due to a persistent right dorsal aorta, with failure to survive of part or all of the fourth right aortic arch. The vascular anomaly is not invariably associated with an aberrant nerve. The nerve may loop round the subclavian in the usual manner, the inferior thyroid, or a right vertebral artery arising from the common carotid. Where the recurrent laryngeal nerve loops round a vessel it is thought that part of the fourth right arch survives and is included in that vessel, and that it is only in total failure of the fourth arch that the nerve passes directly into the larynx. The aberrant recurrent laryngeal nerve may be short and stout, or it may consist of several filamentous strands (Harvey, 1917). It comes off the main trunk of the vagus at about the level of the cricoid cartilage and it may pass either behind or in front of the common carotid artery to enter the larynx directly. In the latter position the nerve would be particularly vulnerable during exposure of the gland at operation (Pemberton and Beaver, 1932). The nerve may be anterior or posterior to the inferior thyroid artery. Work (1941) reported a case in which the anomalous nerve on the right was intimately related to the capsule as it lay in a deep notch on the posterior surface of the gland. Thane (1892) states that the anomaly of the subclavian has been found on the left in a case with a right aortic arch, and therefore it is possible that the aberrant nerve in a very rare case might be found on the left. The incidence of an anomalous right subclavian artery arising from the aorta distal to the origin of the left subclavian has been estimated as 6 in 1,000 cases by Holzapfel (1899), 4 in 1,000 by Thane (1892). A further review of the literature gives the figure of 22 out of 2,169, or roughly 1%.

Discussion and Conclusions

The surgical implications of these findings were discussed. From anatomical considerations alone it was concluded that there was a small but probably irreducible and inherent risk of damage to the recurrent laryngeal nerve in thyroidectomy.

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Professor J. B. Kinmonth said that, following Lahey's suggestion, he had identified the nerves during thyroidectomies for the last ten years. Many of the operations were done at the Surgical Unit at St. Bartholomew's and some of his colleagues also used the method. Most of the patients had their cords examined before and after operation. Using this method they had had only one case of paralysis and that was a temporary one following separation of the nerve from a particularly large adenoma which had displaced it far from its original path. Blind removal of the goitre might have left a permanent palsy.

Mr. A. S. Till said that 300 consecutive personal cases of thyroidectomy for non-malignant goitre had been examined post-operatively by Mr. Gavin Livingstone in Oxford and these showed that 3% had a permanent paresis of one cord and 7% had temporary paresis.

Dismay at this high figure compared with other published figures had led him to identify the nerve in a further series but as the percentage damaged appeared greater he had reverted to the technique of avoiding the nerve unless some special circumstances demanded its exposure.

Mr. J. E. Piercy considered the suggestion that the nerve should be exposed on every occasion to be a dangerous teaching which in itself might lead to its injury. "Know where the nerve should be and search for it where it may be" was a far safer teaching and practice. When undertaking a total thyroidectomy or when removing a posterior marginal adenoma it was perfectly correct deliberately to expose the nerve.

Mr. D. F. Ellison Nash, referring to the "safety" of the upper pole, remarked that he himself had seen, on one occasion, the main portion of the recurrent laryngeal nerve passing between the divisions of the superior thyroid artery at the tip of the upper pole.

Early and First-aid Treatment of Burns [*Abridged*]

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FOLLOWING any trauma there arises (1) the biological response to injury leading to general effects and (2) the local injury leading to both general and local effects.

The biological response.—I beiieve that it is necessary for every surgeon to study this carefully both in respect of immediate and later effects. In simple terms immediately following trauma a neuro-hormonal influence is released. The posterior pituitary releases an antidiuretic hormone acting on the renal tubu'es; the adrenal cortex releases influences which cause profound metabolic disturbances. The changes in renal tubular function are maximal as regards water from the start, but the metabolic changes, although generated from the trauma, are not maximal for some time.

The local injury.—Following external violence of sufficient magnitude the resulting local reactions lead to a disturbance of the fluid distribution causing swelling of the injured tissues. These changes may in turn involve the body as a whole.

Discussing the disturbances of fluid distribution the reduction in blood volume in burnt patients is proportional to the extent of the burn and the loss is spread over the first forty-eight hours and is most rapid in the first eight hours. The reduction in circulating blood volume leads to an early state of anoxia which, in turn, leads to damage of liver and kidney cells. In deep burns there is, in addition, an immediate destruction of red blood cells—evidenced by hæmoglobinuria in some cases.

There is no doubt in my mind of the urgency with which fresh whole blood should be given in deep burns and plasma in superficial burns over 10% of surface area, irrespective of the value of the hæmatocrit. In other words, in fluid therapy "replacement" fluids are given immediately to replace the fluids already lost and to keep pace with further fluid loss. In superficial burns it has been our teaching to administer fluids in the proportion colloid: electrolyte of 1 : 1. Recent observations indicate that in the more extensive deep burns electrolyte should be limited to proportions blood, plasma, electrolyte $2 : 1\frac{3}{4} : \frac{1}{4}$.

Calculators for fluid requirements like the pyrogram are of considerable value as they form a ready guide for prompt treatment. They are intended as guides only.

In addition to the replacement fluids, "requirement" fluids must be given also.

It is most important that in every patient with extensive burns a catheter specimen of urine be examined for pigment. In severe oliguria or anuria consequent upon the renal damage following a large burn, fluid intake must be balanced accurately against output by all routes.

Improvement with fluid therapy is best assessed by hourly urine output. In extensive burns over the first two days the urine output may be reduced but should not necessarily be a cause for alarm. A reasonably satisfactory value for an adult for the first forty-eight hours is 30 to 40 ml. per hour.

Supportive therapy.—Includes morphine, oxygen and penicillin.

Local treatment.—It is important to consider the burnt areas as a wound.

The basic classification in wounds is (*a*) the closed wound and (*b*) the open wound, and in the treatment of all wounds the aim is to convert open wounds to the closed state until healing is accomplished.

In both superficial and deep burns the open and closed wound concept is, in my opinion, the proper approach.

The superficial burn is an "open" wound. The quickest and most certain method of closing it is to allow the plasma exudate to clot. Once this occurs the wound is "closed", irrespective of whether a dressing is applied or not. A dressing by itself never closed a wound. A plasma crust is a biological cover and second only in value to intact skin and it does not matter what organisms are found on its surface as the crust is an all-sufficient dressing until healing is complete.

Consider now the deep burn wound. This is, at the time of receipt, a "closed" wound; the cover is coagulated skin or "eschar". The wound, therefore, possesses its own dressing which remains intact for ten to fourteen days. At this time the living tissues visibly separate from the edges of the eschar; moisture appears at these parts and the wound becomes "open". This open phase must be forestalled by sufficiently early total excision of the eschar and by *immediate* grafting. Excision alone is useless. The excision should be carried out at what the surgeon considers the optimum time for the patient between receipt of the burn and the twelfth day. In the patient with a localized deep burn admitted with little shock it becomes clear that the proper time to excise the eschar and graft is soon after admission. If the deep burn is not excised before the "open" phase, infection can be troublesome because a fresh raw surface has been opened.

It is possible, therefore, to keep a deep burn wound closed until healing is accomplished and infection can thus be eliminated. Infection, therefore, is almost a measure of inadequate surgical treatment and not a natural sequel to a deep burn. Agreed, we cannot always achieve our aims but the surgical challenge remains. It is not a challenge for new antibiotics but for advances in surgery. It has been stated that following removal of an eschar organisms can be cultured. This does not matter if the grafts applied immediately take 100%. We must be surgical clinicians and be guided by surgical results.

Deep dermal burns are by definition superficial burns in so far that certain remaining epithelial remnants are capable of providing final cover. With the considerable dead dermal cell content the lag period of healing in the deep dermal burn wound is prolonged and moist exudate around the third and fourth week encourages infection which leads virtually to destruction of the remaining viable epithelial elements. In many instances, therefore, early excision of deep dermal burns would give much more satisfactory and prompt healing than would delaying tactics.

The distinction, clinically, between superficial, deep dermal and deep burns is difficult. I have found daily colour photographs of some value. Extensive flame burns are commonly deep. The pin-prick test is helpful but not distinctive. One question might be asked, what extent of deep burn could safely be excised in the first twenty-four hours? I cannot answer this as I have not sufficient experience. Caution must be exercised but we must try.

Important possible early complications.—Certain conditions may arise which, strictly speaking, are not complications but a direct result of the burn or resultant reactions.

The first danger is from pressure effects. Circumferential burns of the neck, fingers and upper extremity by their crust or eschar may form an inelastic cover of the part. The œdema which then occurs may lead to a distal ischæmia and, in the case of burns of the neck, pressure on the trachea. We have had in the past two years to perform three tracheotomies within the first eighteen hours. Careful nursing and supervision of burns of the face and neck is an absolute essential, especially over the first day. In addition to the external burn there may be the noxious effects on the mucous lining of the upper respiratory passages. These factors, if present, increase the urgency for tracheotomy.

Circumferential burns of the hands, in my opinion, and circumferential burns of the upper extremity must be carefully watched for distal constriction effects over the first twenty-four hours and this is one of the reasons why I do not advocate cover. In the past two years we have had to carry out multiple incisions on at least 4 patients and then to apply absorptive dry dressings to encourage crust formation and a closed wound. The effects of relieving tension can be dramatic and in no way jeopardize the maintenance of a dry surface.

The second danger is œdema. Control of œdema requires special mention. It forms very quickly and is a natural response to injury. Control should be taught as a first-aid measure, because if it is not treated from the first by posture it can become a troublesome complication.

The third danger is the possible extending of the lag period. The following is a list of "local factors" which, to my mind, extend the lag period and, therefore, delay wound healing: antiseptics, heavy instruments (scrubbing), antibiotics (local), soft paraffin, inadequate or excessive dressings, œdema, too early movement and dead tissue.

Mr. Patrick Clarkson confirmed the value of the Universal Burn Dressing as made to the specifications of the National Research Council of America. This dressing was a composite one of inner fine mesh gauze, absorbent cotton-wool, water repellent cellulose, and sisal. It could be very readily and within three to five minutes applied to trunk and limbs, either as a first-aid measure or as the definitive primary occlusive treatment. The merit of the dressings, in addition to their ease and speed of application, was their high absorbency and the consequent reduction of maceration.

He thought that more stress should be placed on the early assessment of depth of burn. It was depth that chiefly influenced the amount of early red blood cell loss, that made the hæmatocrit an unreliable index of the exact early intravenous fluid requirements, that chiefly determined the need of early blood, and that adversely affected both early and late prognosis. He did not think that formulæ or pyrograms should be taken as anything but approximate guides to the early intravenous fluid needs of patients. The most practicable guides to rate and amount of early fluids were the clinical progress and the urinary output (30 c.c. an hour). The other findings (clinical and laboratory) should be taken when possible and plotted graphically. Together with the clinical state and the urinary output this graph determined the amount of early colloid and electrolyte intravenous infusion. Most patients needed something between 5% and 10% of the body-weight of intravenous electrolyte and colloid in the first forty-eight hours. He also stressed the need of avoiding pure water by mouth to avoid water intoxication and increase in vomiting. Morphia was a bad choice of early opiate as it increased the tendency to vomit. He preferred heroin or Omnopon which should be given intravenously.

Experience of the Stripping Operation for Varicose Veins

By J. B. KINMONTH, M.S., F.R.C.S.

Professor of Surgery, St. Thomas's Hospital, London

THE stripping operation for varicose veins is of great antiquity. It was practised by Galen in the second century A.D. and has been in and out of fashion ever since. In more modern times it had a vogue at the beginning of this century. A wave of enthusiasm for injection treatment then swept it away and it did not become popular again until after World War II.

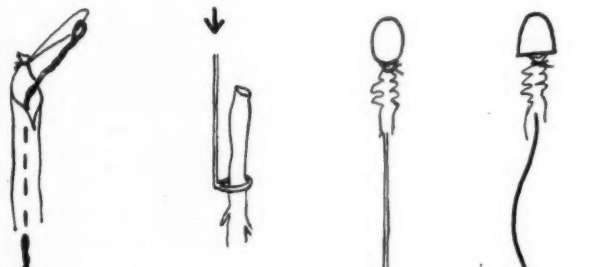

FIG. 1.—Types of vein stripper.

Fig. 1 shows four ways of stripping. Keller's and Mayo's strippers often broke the vein without removing it entire. Babcock's stripper is a very good one. It is passed along the lumen; when it is withdrawn the vein is gathered up against the head and is unlikely to br[eak].

Myer's stripper is the one now most commonly used. It works on the same principle as Babcock's but is flexible instead of rigid and therefore easier to pass through the more tortuous veins. It has a bead at the end which is passed along the vein. The wire part is long enough to reach from the ankle to the groin. It is best to have a set of three, each with a different-sized head. The smallest can be used for shorter lengths of vein in the lower leg, the largest for the wider and longer stretches of vein. When the Myer's stripper is used a standard ligation at the sapheno-femoral junction is first done. The stripper is then passed along the vein which is tied on to it next its head. When the stripper is pulled out the vein "concertinas" against its head. The operation should be done with the patient in the Trendelenburg position. This greatly reduces bleeding. The stripper usually passes more easily from below upwards. This also causes less damage in the leg because less bulk of vein is being pulled through the more compact subcutaneous tissues there. This is important because the saphenous nerve is in close relation to the vein in the leg. For the same reason it is better to use a small stripper in the leg and strip it separately from the thigh. Damage to the saphenous nerve occasionally gives a temporary patch of anæsthesia near the internal malleolus. The amount of hæmorrhage varies from case to case. It is often helpful after stripping to apply a sterile Esmarch bandage for a few minutes before closing the wounds. The Trendelenburg position should be maintained during transit to the ward and afterwards for at least twenty-four hours.

The bogy that has been raised about the stripping operation is that it causes a high incidence of deep thrombosis and embolism. My personal impression has been that the incidence is low but to see if it were really so I have made a small statistical study, and the results are shown in Table I. I am indebted to Mr. Michael Williams, Mr. Bolton Carter and Miss D. Aitken for their help.

PULMONARY EMBOLISM

(1) *Following stripping operations for varices*			
St. Thomas's (1949–1954)	Cases 204	Embolism 1	(0·5%)
St. Bartholomew's (1950–1954)	157	1	(0·6%)
University College (1951–1954, Carter)	237	1	(0·4%)
Mayo Clinic (1947–1951, Myers)	711	3	(0·4%)
(2) *Following general surgical operations*			
St. Bartholomew's (R. S. Murley, 1950)	Cases 1,289	Embolism 6	(0·5%)
Mayo Clinic (1928–1940)	158,200	—	(0·6%)

The first group consists of patients who have undergone the stripping operation for varicose veins. The rates for embolism at these London Teaching Hospitals and at the Mayo Clinic are remarkably consistent and work out at about 0·5%. Mr. F. N. Glover tells me that they have done a similar number of cases at Guy's Hospital. There was one case of thrombosis, but no embolism. The second group consists of two series of general surgical operations. The embolism rates of 0·5% and 0·6% are lower than most of those reported. Indeed, Mr. Murley's series was one in which special efforts were made to keep the incidence as low as possible. I think it is therefore fair to say that the incidence of embolism after the stripping operation is no higher than after that for other surgical operations, and in fact probably somewhat lower.

CLINICAL RESULTS

It is extremely difficult to find a statistical method of comparing the results of stripping with other forms of treatment of varices and I have not attempted it. My impression is, however, that it gives better results with fewer recurrences and I think that has been the experience also of other surgeons who have used it.

Mr. **F. B. Cockett:** I should like to point out that stripping of the great saphenous system from a point just anterior to the internal malleolus, to the groin (as is usually done), does not avulse or destroy the perforating veins in the lower half of the leg. There is now a good deal of evidence that destruction of the valve and incompetence in one or more of these perforating veins is a very common cause of the lesions known as varicose or gravitational ulcers. Thus the stripping operation may not necessarily be of any extra benefit to these cases, as it leaves the incompetent perforating veins intact (*see* Cockett, F. B. (1953) "The Ankle Blow-out Syndrome. A New Approach to the Varicose Ulcer Problem", *Lancet*, i, 17).

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Section of Dermatology

President—REGINALD T. BRAIN, M.D., F.R.C.P.

[*December* 16, 1954]

Lichen Planus Pemphigoides.—B. SCHWARTZ, M.D.

Mr. A. A., aged 45. Cabinet maker.

Apart from the history of occasional boils he was completely free from skin disease until August 1954, when he developed a generalized irritation and rash over the trunk and limbs.

There was no relevant previous personal or family medical history and he was taking no drugs or medicines.

A dermatological examination in September 1954 revealed: "On the upper arms, right more than left, there were plaques of violaceous lichen planus composed of aggregated papules. On the sacrum there were lesions of lichen planus hypertrophicus. On the lower legs and thighs there were lichen planus papules and plaques and relics of vesicles and blisters on the shins. There was one lesion on the penis. The mouth was clear. There was no adenopathy and the liver and spleen were not palpable."

Investigations.—W.B.C. 4,450 per c.mm. Normal differential count. E.S.R. 2 mm. in the first hour (Westergren). W.R. negative. Urine normal. X-rays: Chest and sinuses normal (Dr. L. Sefton).

Local applications and sedatives had no effect and irritation increased markedly.

On 28.10.54 he showed a generalized polymorphic symmetrical eruption of the trunk and limbs consisting of erythematous lesions, gyrate urticarial patches, scratched papules, vesicles and bullæ which had been present some two to three weeks. The lesions were most numerous on the legs, buttocks and shoulders. The vesicles and bullæ which contained clear fluid, varied in size from 1–2 mm. to 1–3 cm. in diameter and were most profuse on the limbs. They showed a tendency to herpetiform grouping, particularly on the thighs and shoulders (Figs. 1 and 2), and were seen to arise in association with erythematous lesions, with papules and on apparently normal skin. On the sacral area and on the penis there were typical lichen planus lesions (Fig. 4). The mouth was clear. A blood count showed a polymorph leucocytosis with no eosinophilia.

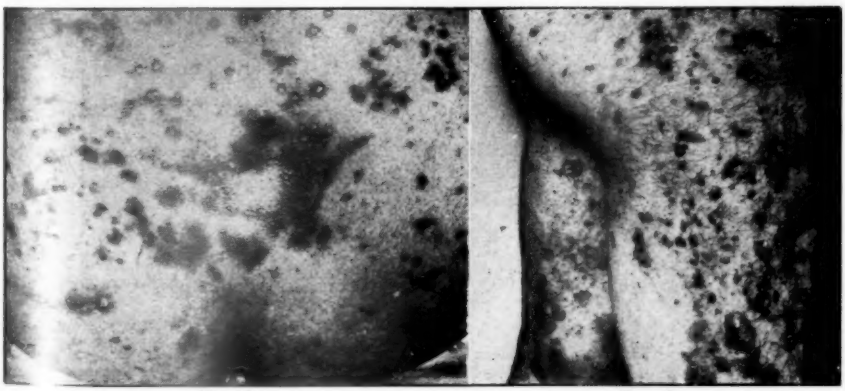

FIG. 1. FIG. 2.

s. 1 and 2.—One week after treatment with ACTH. Showing residual pigmentation and tendency to herpetiform grouping of lesions on buttocks (FIG. 1) and thigh (FIG. 2).

iagnosis of dermatitis herpetiformis with lichen planus was made and trial treatment wit ulphapyridine and subsequently with diaminodiphenylsulphone was given. This fail to control the lesions or the increase in burning and irritation. Bullæ became more pro e and larger particularly on the distal parts of the limbs where unruptured tense bul 7–10 cm. in diameter, were seen (Figs. 3, 5 and 6). There was no pyrexia, no abnormal ade pathy and the liver and spleen were normal.

Ju

Investigations.—Hb 96% (14·2 grams %). W.B.C. 12,600; polys. 81%, lymphos. 4%, monos. 3%, eosinos. 12% (1,452/c.mm.). E.S.R. 7 mm. in the first hour (Westergren).

Scraping from floor of blister: No acantholytic cells found; mostly eosinophils and mononuclear cells. Biopsy of blister (arm): The histology is that of a subepidermal bulla containing a few eosinophils. There is also a marked perivascular infiltration consisting of round cells and a few eosinophils.

FIG. 3.—Large bulla left wrist.

FIG. 4.—Lichen planus of penis with bullæ arising on normal skin.

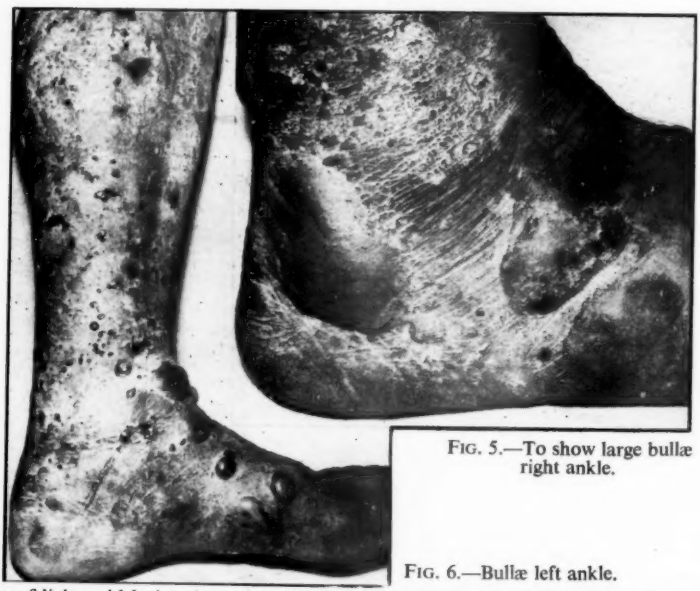

FIG. 5.—To show large bullæ right ankle.

FIG. 6.—Bullæ left ankle.

Biopsy of lichenoid lesion (sacral area): The lesion shows hyperkeratosis with granulosis patchy and irregular acanthosis. In one place the serrated appearance of the papilla body is striking. In some places there are epidermodermal clefts which have led to the appearance of lakes situated between the epidermis and dermis. The infiltrate is sharply defined as a subepidermal band consisting of round cells. The histology suggests lichen planus (Dr. H. Haber).

He was admitted to hospital under Dr. Stephen Gold and treatment with a saline drip containing ACTH 20 units and heparin 1,000 units, given daily for eight hours, was commenced on 29.11.54. This produced complete control of the symptoms within forty-eight hours. Bullæ dried up, and lichen planus lesions flattened, leaving widespread local hyperpigmentation in both lichen planus and bullous areas (Figs. 1 and 2). A blood count on 6.12.54 still showed a leucocytosis (total 15,600; polys. 65%, lymphos. 28%, monos. 2%, eosinos. 5%). Treatment with ACTH is being continued.

Comment.—The occurrence of vesicles and bullæ in lichen planus is not uncommon. In general these vesicles arise on lichen planus papules, are not extensive and are of short duration. There appears to be a group, however, where the bullæ are an extensive and dominant feature and it was for this group that Kaposi in 1892 (*Arch. Derm. Syph., Berl.*, 24, 344) coined the term "Lichen-Ruber Pemphigoides".

The salient features of the few reported cases of this condition seem to be: (1) An outbreak of widespread lichen planus in scattered lesions and plaques. (2) An abrupt bullous attack with bullæ most numerous on the extremities and a tendency to grouping. (3) The bullæ are thick-walled, rupture with difficulty and vary in size up to 7 to 10 cm. in diameter. They occur on lichen planus lesions, erythematous lesions or on normal skin. (4) There is an associated polymorph leucocytosis with some increase in eosinophils.

Whether or not on the grounds of this clinical picture one should accept lichen planus pemphigoides as an entity in itself or look on it as another variant of lichen planus bullosa is a problem for discussion. Or should we postulate here, as Pautrier did in 1933 (*Bull. Soc. franç. Derm. Syph.*, 40, 1137) when he described a similar case and as I did myself at first, the presence of two dermatoses, lichen planus and dermatitis herpetiformis, in association. The occurrence of vesicles on lichen planus lesions is a normal histological possibility but can bullæ which arise on normal skin be considered as lichen planus?

I personally am in favour of calling this lichen planus pemphigoides and not lichen planus with dermatitis herpetiformis, firstly, because of the rapid response to comparatively small doses of ACTH—dermatitis herpetiformis usually requires much larger doses to bring it under control; secondly, the lack of any response to sulphapyridine is also against a diagnosis of dermatitis herpetiformis, and, lastly, the healing of all the lesions, including the large bullæ, has left a residual pigmentation which is much more suggestive of lichen planus.

Dr. H. Haber: A characteristic lichen planus papule shows the following histology: There is solid hyperkeratosis, patchy parakeratosis acanthosis and serrated appearance of the papillary body. Immediately under the epidermis there is a sharply defined dense infiltration consisting of round cells and a few histiocytes. The infiltrate invades the lower parts of the epidermis leading to blurring of the epidermodermal junction and also to œdema of the basal cell layer. The disturbance created by the œdema of the basal cell layer leads to pigmentary incontinence as shown by the presence of many chromatophores heavily laden with melanin. The œdema also leads to the formation of characteristic clefts. If the exudation attains wider proportions the clefts can be widened to produce subepidermal bullæ. But bullæ may also be formed under the stratum corneum. It is known that bullæ may also appear in cases of acute lichen planus independent of pre-existent papules. This is shown clearly in the case under discussion. The case is typical lichen planus pemphigoides. Under certain circumstances bullæ may occur in chronic lichen planus of the legs. Here the lichen planus papules undergo atrophy. The epidermis is reduced to a few layers only. The papillary body shows marked sclerosis of its collagen. The infiltrate is mild. The epidermodermal cohesion, however, has suffered. Stasis leads to the accumulation of fluid and total separation of the epidermis from the dermis to produce a subepidermal bulla. Such a case has been shown by Dr. L. Forman and myself (1950, *Proc. R. Soc. Med.*, 43, 171).

Median Lethal Granuloma of the Face, Treated by Radiotherapy.—R. G. Howell, M.R.C.P. (for G. B. Mitchell-Heggs, O.B.E., F.R.C.P.).

Mr. P. L., aged 60, complained of progressive painful swelling of the nose with obstruction to breathing and an offensive nasal discharge for one year. In September 1954 the nose was uniformly swollen and red, with granulations sprouting in the nasal fossæ. The adjacent lip and cheeks became swollen. There was a chronic offensive purulent nasal discharge and recurrent exacerbations of acute inflammation of the nose. His general condition gradually deteriorated. He has been under observation for pulmonary tuberculosis for some years with old healed fibrotic lesions at both apices.

Investigations.—Urine normal. Chest X-ray: Old healed bilateral apical tuberculosis which has not changed in the past year. Tomograph: No cavitation seen. Sputum: No acid-fast bacilli found in three specimens. Blood: Hb 70%; R.B.C. 3,200,000; C.I. 1·0; M.C.D. 7·0μ; W.B.C. 9,000 (polys. 63%, eosinos. 2%, lymphos. 31%, monos. 4%). Blood W.R. negative. Plasma proteins: Total 6·5; albumin 3·5, globulin 3·0 grams/100 ml. Culture from nose: *Staph. aureus* and hæmolytic streptococci.

Histology of tissue from nose.—19.2.54: Chronic inflammatory reactions characterized by lymphocytes and plasma cells. 3.9.54: A non-specific granulomatous lesion composed mainly of lymphocytes and round cells.

Treatment and progress.—This patient has been for the most part under the care of Mr. Ian Robin. Exacerbations of acute infection responded to streptomycin and Terramycin at different times. Calciferol and streptomycin produced no improvement.

In September 1954 he was admitted to St. Mary's Hospital when his general condition was very poor and he was deteriorating rapidly.

The following X-ray treatment was advised and carried out by Dr. M. Hulbert—11 daily treatments of 200 r lesion dose, at 220 kV, 2 mm. Cu H.V.L., 12·5 mA, 50 cm. F.S.D.; using two lateral opposing fields 10×8 cm. There was a marked regression of the lesion and there now appears to be no evidence of an active inflammatory process.

Comment.—Since McBride wrote of a case of "Rapid Destruction of the Face" in 1897 (*J. Laryng.*, **12,** 64) there have been many accounts under different names of similar non-specific chronic inflammatory lesions of the face producing marked destruction of tissue and ultimate death of the patient. The title of this case was used for its completeness in describing the clinical picture.

Radium and X-rays have been used in treatment with variable results.

Dr. I. B. Sneddon: I would accept the diagnosis as the case is very like the one Dr. J. Colquhoun and I published in 1952 (*Brit. med. J.*, **i,** 298). I should like to take this opportunity of reporting that although the original lesion in the nose of our patient cleared with treatment the granulomatous process recurred in the pharynx eighteen months later and after several months the patient died. At autopsy no abnormality other than the granuloma could be found. There was no evidence of metastasis or of periarteritis nodosa.

Since then I have had another case, a woman of 35, who had had two attacks both associated with pregnancy. After a long period in hospital with no response to antibiotics the granuloma was controlled by X-ray therapy in a dose of 2,500 r. By the time the disease had been stopped she had lost her entire central face. She has a space from the frontal bone to her mandible. Now eighteen months after the X-ray treatment the disease is quiescent. She is well in herself and runs a public house serving behind the bar wearing a yashmak. ACTH was tried at one stage but produced such a rapid spread of the inflammatory reaction that it had to be stopped.

In my opinion the granuloma is a peculiar tissue reaction of the host similar to a pyogenic granuloma produced by infection with pyogenic organisms.

Dr. Brian Russell: Could this not be a non-specific granuloma or perhaps lupus of the nose with secondary infection? Good results used to be obtained with X-rays in lupus, which might explain the favourable result in this case.

Dr. Hugh Gordon: This case reminds me of one which I saw at the Royal Marsden Hospital in 1952. The patient was said to have had a chronic boil in his left nostril which had been present for about a month. This had not responded to large doses of penicillin by injection and an antibiotic locally. On examination we had not the slightest doubt that the lesion was an epithelioma. A section was taken and a plaster cast prepared for the ensuing radiotherapy which was in fact ordered. We were somewhat startled when the pathological report came through "simple granuloma, no sign of malignancy". A second biopsy and a Wassermann both proved negative.

At that time I saw Dr. Sneddon's article in the *British Medical Journal* describing his case of a malignant granuloma of the nose and I felt that our case must be an example of this condition. Consequently we put him on vast doses of Chloromycetin. Unfortunately, however, the granuloma steadily increased in size, and the whole nose became swollen and painful. I admitted him to hospital and asked an E.N.T. colleague to scrape out thoroughly the whole lesion under a general anæsthetic. Pathological examination was again negative for carcinoma and bacteriologically *Staphylococcus aureus* only was found which was said to be penicillin-sensitive. I asked Dr. Sneddon's advice, and he advised radical surgery.

Operation.—Mr. W. A. Mill, at the Royal Marsden Hospital, removed the entire nose as far back as the ethmoid processes and part of the upper lip. Sections performed disclosed an undoubted carcinoma which had not as yet invaded bone. The patient after various plastic procedures has been fitted with a prosthetic nose and is tolerably comfortable and well.

Our chief regret is that we did not disregard the first pathological report and did not treat him with 6,000 r in split doses as originally intended since by so doing we would almost undoubtedly have cured him and saved his nose.

Dr. R. D. Sweet: I have had only one case, much more rapid in its course than those mentioned, as the total history to death was only five months. There was no response to 1,800 r nor to ACTH. Both cheeks, the nose and the whole of the palate were involved but a thorough search after death yielded no evidence of any underlying neoplasm. The most impressive feature of these horrible cases is the utter lack of any form of resistance—no leucocytosis, no fever and even no pain, as witnessed by Dr. Howell's patient. This is in contrast to what Dr. Brian Russell would surely expect of a streptococcal infection.

The following cases were also shown:

Darier's Disease.—Dr. F. RAY BETTLEY and Dr. H. HABER.

(1) **Case for Diagnosis. ? Lupus Erythematosus Profundus.** (2) **Pityriasis Rubra Pilaris.**—Dr. R. H. MARTEN (for Dr. F. RAY BETTLEY).

Angiokeratoma.—Dr. E. N. M. JOHNSTON (for Dr. E. W. PROSSER THOMAS).

(1) An Early Squamous Cell Carcinoma (Five Weeks). (2) An Early Squamous Cell Carcinoma (Five Weeks) Clinically Simulating Molluscum Sebaceum. (3) Scleroderma with Auricular Fibrillation.—Dr. E. J. MOYNAHAN.

[*January* 20, 1955]

Kaposi's Idiopathic Hæmorrhagic Sarcoma.—J. E. M. WIGLEY, M.B., F.R.C.P., D. L. REES, M.D., M.R.C.P., and Professor W. ST. C. SYMMERS, M.D.

Mrs. J. R., housewife, aged 73. Czechoslovakian.

FIG. 1.—Distribution of confluent lesions on legs.

History.—She was well until three years ago when gradual swelling of the ankles appeared; this increased and slowly spread to involve the legs and knees. At about the same time nodules began to appear in the skin about the ankles. These started as pink nodules which became larger and turned in colour to the present reddish-purple of her older lesions. Further lesions appeared progressively involving the legs, arms, neck and trunk. New lesions were observed to appear during her recent period in hospital.

She had a winter cough and dyspnœa on effort but no chest pain. She had had some abdominal discomfort recently.

Past history.—Typhus fever; 1943—pneumonia; 1951—course of gold injections for "rheumatism."

On examination.—Elderly woman. No adenopathy or clinical anæmia.

C.V.S.: No signs of congestive failure. B.P. 230/105.

Respiratory system: No clubbing or tracheal deviation. Impaired percussion note and diminished air entry in left third interspace anteriorly.

Skin: Firm pitting œdema of legs up to lower thighs. Numerous purplish, raised, indurated nodules on ankles and legs becoming coalescent about ankles (Fig. 1) with a few similar lesions on arms, neck and trunk.

Urine: Protein—a trace. A few red and white cells.

Investigations.—Hæmoglobin 88%; W.B.C. 9,700

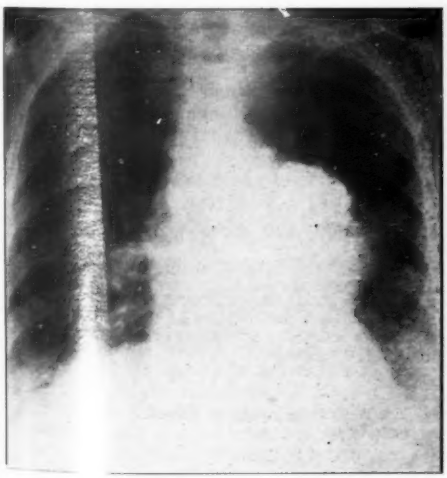

FIG. 2.—Straight X-ray of chest showing lobulated calcified tumour in the left hilar region.

FIG. 3.—Left lateral view of chest showing position of tumour in anterior mediastinum.

(polys. 50%, lymphos. 42%, monos. 8%). B.S.R. 35 mm. in first hour (Westergren).

Chest X-ray: "Lobulated tumour in left anterior mediastinum which shows dense calcification and transmitted pulsation from the heart (Figs. 2 and 3). No narrowing of left main bronchus. Appearances suggestive of hamartoma. Dermoid cyst is another possibility."

Skin biopsy: Side by side in the dermis are two small tumour nodules (Fig. 4). The larger consists of close-set spindle cells intertwining amongst developing capillaries which are often distended with blood and there is much interstitial hæmorrhage (Fig. 5). The smaller nodule is a similar but older lesion showing extensive fibrosis and hyaline change with blood pigment scattered through it. These appearances are characteristic of two of the stages in the development of lesions of Kaposi's disease (multiple idiopathic hæmorrhagic and pigmented sarcoma, i.e. a variety of angiosarcoma).

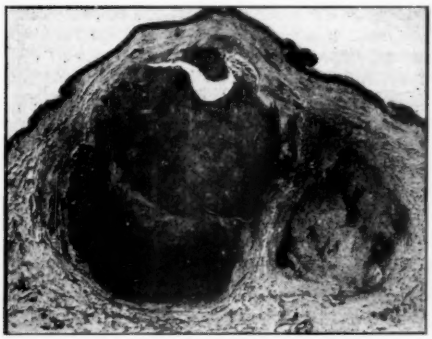

FIG. 4.

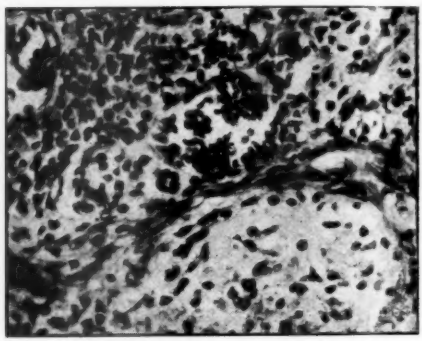

FIG. 5.

FIG. 4.—Low power. Showing recent dermal nodule on the left and old fibrosed nodule on the right.

FIG. 5.—High power. Showing cytology of more recent nodule.

Comment.—This patient, a Czech of Jewish extraction, is a native of that part of Europe from which come the majority of the cases of Kaposi's sarcoma reported in the literature (Becker and Thatcher, 1938).

Her cutaneous lesions are characteristic of those described by Kaposi (1895), but it is interesting to speculate on the relationship between the mediastinal tumour which is present and her cutaneous lesions. Most probably the tumour in the chest is in fact a dermoid, as suggested in the X-ray report. However, cases of large isolated tumours with the histology of Kaposi's sarcoma have previously been reported involving the auricles (Weller, 1940) and it is possible that the chest lesions in this case may prove to be of a similar nature.

The rather infiltrated œdema of the legs which is present and which has been observed before in similar cases is probably the result of diffuse infiltration of tumour tissue involving the lymphatics and possibly also the regional lymph glands. It was unaffected by a long period of rest in bed.

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Dr. Peter Smith: Following radical mastectomy a rather similar angiosarcoma may develop in an œdematous upper limb (Stewart-Treves syndrome). The fact that œdema of the leg so often precedes the lesions of Kaposi's disease makes one wonder whether the œdema might have some causal relationship to the development of these angiomatous tumours.

The following cases were also shown:

(1) **Granuloma Annulare Associated with Psoriasis.** (2) **Erysipelatoid of Cheek.**—Dr. R. T. BRAIN.

Congenital Ichthyosis.—Dr. A. A. MASON (introduced by Dr. KATHRYN COHEN). (A report of this case appeared in the *British Medical Journal*, 1952, ii, 422, and a further note will probably also appear in the *British Medical Journal*.)

Section of Obstetrics and Gynæcology

President—FREDERICK W. ROQUES, M.D., M.Chir., F.R.C.S.Eng., F.R.C.O.G.

[*January* 28, 1955]

Endometriosis of the Rectovaginal Septum (Three Cases).—EDWARD COPE, M.D., M.R.C.O.G.

Although the many reviews of large series of cases of endometriosis mention the rectovaginal septum as a common site and the one most difficult to treat, actual case histories since the period immediately following Lockyer's (1913) classical case are few, and treatment is but scantily discussed. The following 3 cases illustrate the problems of treatment and stimulate thought on the pathogenesis of the disease.

Case I.—A para-2, aged 43, whose younger child was 15 years old, presented with a painless abdominal swelling. She had no dysmenorrhœa, dyspareunia or intestinal symptoms.

Bimanual examination revealed a large fibroid uterus. Attached to its posterior surface was a semi-solid swelling which filled the pouch of Douglas, and extended deeply into the rectovaginal septum. The rectal mucous membrane was intact.

Laparotomy revealed a uterus grossly enlarged with fibroids, fixed to the back of which was a tumour of the left ovary the size of a tennis ball. The bowel and omentum were firmly adherent to the back of the uterus and ovarian tumour. The tumour was freed to reveal a solid mass below it, extending down into the rectovaginal septum which was cemented to the cervix and vagina in front, and the rectum behind.

Total hysterectomy with removal of the appendages and a cuff of vagina was performed, the mass being dissected away from the rectum exposing a considerable area of rectal mucosa. This was oversewn and the patient made an uneventful recovery.

The solid part of the ovarian tumour was a fibroma, and the rest a simple cyst; the mass from the rectovaginal septum was a typical adenomyoma.

Case II.—A para-3, aged 32 years, the youngest child being 7 years old, complained of intermenstrual bleeding and rectal pain on intercourse. She had normal painless menses, and no intestinal symptoms. Examination revealed an indurated area in the posterior vaginal fornix, the mucous membrane over it showed the typical blue spots of endometriosis which bled on touching. The uterus and appendages were normal. Biopsy confirmed the diagnosis. She was given methyl testosterone 30 mg. daily for a month, and the lesion disappeared. The dose was repeated daily for a fortnight during the following month, and for a week during the third month. Six weeks after all treatment was stopped there was still no evidence of the lesion. Her periods were normal throughout the treatment.

There is not a large literature on the androgen therapy of this condition. The reported response varies from complete disappearance of symptoms with considerable reduction in tumour size (Massé, Traissac and Dax, 1946), to only slight alleviation of symptoms with minimal reduction in tumour size even with massive dosage (Wilson, 1940).

I have found no other case in which the tumour disappeared completely.

Case III.—A para-1, aged 38, whose child was 6 years old, complained of contact vaginal bleeding. She had no dysmenorrhœa, dyspareunia, or bowel symptoms.

Pelvic examination revealed a large indurated mass in the rectovaginal septum, extending half-way down the vagina and out into the pelvic cellular tissues, reaching the ischial spine on the left side. The typical blue spots of endometriosis were present in the posterior fornix and bled on touching, the rectal mucosa was intact.

Biopsy showed endometriosis in the proliferative phase, though the endometrial curettings were in the secretory phase. Methyl testosterone 10 mg. was given daily for seven weeks without effect. She was deeply worried about the condition, and felt that it was interfering with her married life. She was adamant that she did not want any more children.

An artificial menopause was effected using a central dose of 700 r. The choice of deep X-ray therapy was made because the diagnosis was proved; the lesion could not be extirpated without removal of the rectum; and the lesser operation of removing the uterus and ovaries, leaving the mass to regress, would only do the same as deep X-ray therapy, which from her point of view, would leave the genital tract intact. Seven months after treatment, even though her periods had stopped, the symptoms and physical signs were unchanged.

Repeat biopsy and endometrial curettage revealed active endometriosis in the rectovaginal septum in the presence of a completely atrophic endometrium. A waiting policy was adopted, and now seventeen months after treatment although she has had no periods, she still has symptoms, though the bleeding is less severe, and the mass remains unchanged.

Discussion.—The treatment of this condition depends upon the age of the patient, the extent of the lesion and associated diseases. If the patient fails or is unwilling to become pregnant, it would seem that androgen treatment should always be tried as it may cure the

lesion as in Case II, or reduce it to an operable size (Miller, 1944). If it fails and the patient is young, and the lesion not too extensive, a conservative operation should be done, excising the lesion if necessary by the abdominovaginal technique of Ahumada and Nogues (1946).

If it is too extensive for conservative surgery and particularly if there are associated conditions, radical surgery should be done as in Case I, removing the mass for biopsy to exclude associated carcinoma of the rectum, or even malignant change in the endometrium. If the mass cannot be removed, and adequate biopsy can be made through the vaginal fornix, then deep X-ray therapy would seem the best method and has, as described by Hays and Portman (1951), given better results in extensive endometriosis than radical surgery.

Unfortunately, as Case III shows, ablation of ovarian tissue with deep X-ray therapy may fail to cure the condition in a reasonable time, and the atrophic condition of the endometrium does not give reason to suppose that operative removal of all ovarian tissue would have been more successful, nor does it indicate a significant extra-ovarian source of œstrogen.

Pathogenesis.—In Case III we had, before radiation, proliferative phase endometriosis associated with a secretory endometrium—a not unusual finding; but we also had, after the radiation, a continuation of the proliferative phase endometriosis with an atrophic endometrium, a condition not previously reported.

Endometriosis is not considered to be a true neoplasm as it is not circumscribed, has no capsule, reacts to hormones like normal endometrium, and is too widespread to be benign, and not invasive enough to be malignant. A capsule is not part of a neoplasm, it is merely the surrounding tissues reacting to compression.

Endometriosis, if it did not bleed, would compress the surrounding tissues as it grew, but because it bleeds it sets up a foreign body tissue reaction more fierce than that of mere compression, and we get, not a capsule, but massive surrounding fibrosis. The lesions, like fibroids, are multicentric, and are derived from a closely allied tissue. The occurrence of fibroids in over 50% of cases of endometriosis and the association of myometrium and endometrium in adenomyomata indicates that these are allied slow-growing tumours.

I contend that the variable response of endometriosis to hormones can only be explained by considering the condition as a neoplasm arising from multicentric foci, the different responses being due to the neoplasia occurring at different levels of differentiation.

ACKNOWLEDGMENTS.—I should like to thank Mr. Mitchell for permission to publish the second case, and Dr. W. Whitelaw for preparing the slides and sections.

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Adenomyosis of the Uterus Complicated by Tuberculosis.—BRAITHWAITE RICKFORD, M.D., B.S., F.R.C.S., F.R.C.O.G.

History.—A nulliparous married woman of 48 complained of having had menorrhagia for a year. Past history good except for a cholecystectomy three years previously.

On examination.—The uterus was retroverted and sufficiently large to fill the pelvis, and a diagnosis of fibroids was made. On admission there was a moderate degree of pyrexia, for which no satisfactory cause could be found, in spite of a full investigation.

Operation.—The uterus was found to be retroverted and markedly enlarged by an anterior wall tumour. The tubes were slightly enlarged and, together with the ovaries, lay beneath the tumour deep in the pelvis. They were grossly adherent to the rectum and peritoneum. With considerable difficulty the tumour and appendages were separated from neighbouring structures and a subtotal hysterectomy with removal of both appendages was completed. The cervix was not removed as there was great risk of damaging the adherent rectum and colon. The gross appearance of the uterus suggested a large intramural fibroid. On opening the tumour, however, the cut surface revealed multiple small abscesses from which thick yellow pus was oozing. The endometrium was thickened and of a yellow colour suggesting caseating tuberculosis.

Streptomycin and PAS were given after the operation and a transfusion was also necessary. Recovery was uneventful and the patient is fit six months later.

Microscopy.—"Myometrium shows extensive adenomyosis with multiple tuberculous foci. Many of these are large and caseous obliterating the adenomyosis. Endometrium shows extensive tuberculous lesions. Smears and cultures from the pus were positive for *Myco. tuberculosis.* Guinea-pigs inoculated with myometrium and pus were also positive for tuberculosis."

Placenta Accreta.—A. L. T. EASTON, F.R.C.S., M.R.C.O.G.

Lower segment Cæsarean section was performed at the 36th week on a primigravida aged 34 for recurrent hæmorrhage of unknown cause. Soft-tissue placentography had indicated the placenta to be in the upper segment posteriorly, but at operation it was found to lie beneath the anterior wall of the uterus reaching down almost to the incision in the lower segment. As it would not deliver of its own accord it was, with great difficulty, removed manually, there being no plane of cleavage between the placenta and the uterine wall. Despite the use of oxytocics and with a contracted uterus, bleeding continued and her condition deteriorated steadily. Bimanual compression failed to control the bleeding and so the decision to perform immediate hysterectomy as a life-saving measure was taken. A rapid intravenous transfusion of five pints of blood was given by means of hand rotor pump. This produced an improvement in her general condition which was maintained after supracervical hysterectomy.

Commentary.—Placenta accreta was first recognized in the sixteenth century and systematically recorded by Irving and Hertig (1937) in the United States of America: on an average the incidence is said to be 1 : 31,000 deliveries.

Four different types are described, partial, total, increta and percreta, according to the depth of penetration of the uterine muscle.

The typical histological changes are; absence of the decidua spongiosa and a defective or absent decidua basalis (Fig. 1), with hyaline fibrosis of the adjacent myometrium (Fig. 2). The resultant loss of contractile power accounts for the continued bleeding in these cases.

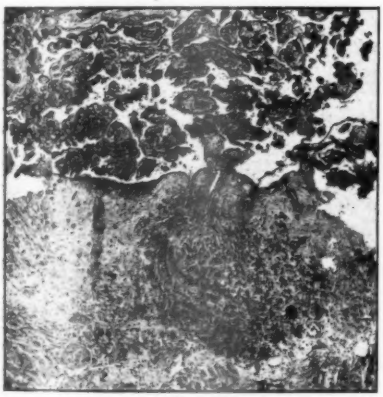

FIG. 1.

FIG. 2.

FIG. 1.—Section taken from the uterine wall at the placental site showing villi above, absence of decidua spongiosa, and defective decidua basalis. The latter is represented by isolated clumps of decidual cells only (×20).

FIG. 2.—Section from an adjacent area showing villi above and to the left of centre; below this, in the midst of muscle that has undergone hyaline fibrosis, is a blood sinus. Elsewhere fibrosis of the muscle can clearly be seen (×20). (Courtesy of Professor R. W. Scarff, Dr. A. C. Thackray and Dr. P. Andrews).

Endometrial damage, either pathological or by the curette, is held by some to predispose to this condition. It is interesting to note that this patient had been curetted three times in her life for various reasons.

Implantation where the decidual reaction is poor, such as the lower uterine segment, also favours undue penetration and so placenta accreta and prævia show an association.

Manual removal *per vaginam* carries with it the highest mortality, figures of between 60% and 72% being quoted. Most are agreed that abdominal hysterectomy is the safest treatment whilst it has been suggested in some quarters that no such attempt should be made to remove such a placenta. In 7 such cases both patient and uterus survived (Burke, 1951).

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Uterine Cyst.—W. G. MILLS, F.R.C.S., M.R.C.O.G.

Apart from cystic degeneration in myomata and cystic dilatation of cervical mucous glands, a cyst of the uterus is a comparative rarity. The specimen shown was taken from a patient aged 28, para-1, who complained of daily spotting for three months following an alleged abortion. The bulky uterus was curetted and a tumour located having the appearance of a submucous myoma about 3 in. diameter. Urine was sent for biological assay in case a chorionic carcinoma was present and at laparotomy soon afterwards the tumour was found to be cystic. Local excision was difficult and hæmorrhagic and the right fallopian tube was damaged. The cyst was opened (Fig. 1) and found to be an unruptured ectopic pregnancy that had developed in the interstitial part of the right tube and had undergone cystic molar degeneration. The patient made a good recovery and soon resumed normal periods. The pregnancy test was reported as negative despite the presence of much chorionic tissue in the wall of the cyst. It is presumed that the activity of this had been sufficient to suppress the menstrual cycle for the previous three months.

FIG. 1.

Carcinoma of Fallopian Tube (Three Cases).—W. G. MILLS, F.R.C.S., M.R.C.O.G.

I wish to comment upon three aspects of this condition in which current opinion might seem to be misleading: (1) That this malignant growth is extremely rare. (2) That preoperative diagnosis is seldom possible. (3) That the poor prognosis is due to early local spread in the pelvis.

(1) Although only 100 cases were collected in 1910 and a mere 450 in 1947, I have myself operated upon 3 cases in the course of about 600 hysterectomies in five years. These cases are now reported.

(2) Regarding diagnosis, it was made in only the first of these cases owing to the associated pathology in the other 2. The first patient was aged 40 and her only pregnancy had ended in abortion. She complained of intermittent yellow discharge and on examination a jet of bright yellow fluid was seen to emerge from the external os. A fixed swelling was palpable in the left fornix. At operation there was bilateral hydrosalpinx with an early carcinoma in the isthmus of the left tube.

The second patient, aged 65, para-3, had postmenopausal bleeding. A large submucous

FIG. 1.

myoma was found at curetting and this concealed the graver pathology, for laparotomy showed an early carcinoma in the ampulla of the right tube (Fig. 1).

The third patient, a nullipara aged 56, complained of a resumption of the menses after three years' amenorrhœa. Two pelvic tumours were diagnosed as fibroids but operation revealed bilateral tuberculous pyosalpinx with papillary adenocarcinoma developing in the closed cavity on the left side.

(3) Regarding prognosis, it was instructive to find the first patient dying from massive abdominal secondaries with virtually a clear pelvis. The second patient, despite an early growth, had a high lateral aortic lymph node removed which was found to contain secondary growth. It is therefore concluded that early lymphatic spread causes the ultimate death of these patients rather than any pelvic recurrence.

Ectopic Pregnancy with Pelvic Tuberculosis.—G. DALLEY, M.R.C.S., L.R.C.P.

The specimen was a nearly complete fœtal skeleton which had been removed piecemeal from the rectum of a primigravida. The history is as follows: She was aged 40 and at age 17 she had had pleurisy and excision of glands of neck since when she had been in good health. She was admitted to hospital after twenty-two weeks' amenorrhœa when the uterus appeared of the appropriate size but there was a large swelling behind and to the left of it. X-ray showed a fœtus of correct age with early maceration. The swelling continued to grow rapidly and laparotomy was performed when the mass was found to be growing from the left side of the pelvis retroperitoneally and quite inoperable. Her condition deteriorated and a posterior colpotomy was performed for diagnostic purposes. The fluid proved sterile and contained no malignant cells. Later culture showed a growth of *Myco. tuberculosis*. Treatment was started of streptomycin 1 gram and isoniazad 300 mg. daily. Her condition gradually improved and the mass diminished in size. After two months she was transferred to a sanatorium for further treatment. Six months later she returned for removal of this mass but examination showed fœtal bones projecting into the rectum. These were removed at several attempts and the latest X-ray showed no fœtal bones in the pelvis. She is now quite well but has occasional watery diarrhœa and it is proposed to continue conservative treatment.

Double Chancre in the Puerperium.—GEORGE BANCROFT-LIVINGSTON, M.D., F.R.C.S., M.R.C.O.G.

Patient was a married woman, aged 32, who was first seen on 28.10.54, six weeks after normal delivery of a full-term living infant. She was complaining of vulval discomfort, and on examination was found to have a small ulcer on the left labium majus and a few shotty glands in both groins. Examination of the cervix revealed an area of necrotic ulceration of the posterior lip. There was no other gynæcological abnormality.

Dark-ground examination of both the vulval and cervical ulcers was negative, as was the Wassermann and gonococcal complement-fixation test.

She was admitted to hospital where four further dark-ground examinations from both lesions proved negative and swabs showed mixed growth of organisms only. Ten days after admission a piece of the cervical ulcer was removed for histological examination because of the possibility of carcinoma. This, however, showed marked epithelial hyperplasia accompanied by intense inflammatory changes. Five days later the W.R. became strongly positive, but lumbar puncture showed normal cerebrospinal fluid. She thereupon received a course of penicillin treatment and both the cervical and the vulval ulcer healed rapidly.

The baby was examined and found to be well and serologically negative and her husband although clinically normal, showed a strongly positive W.R. He had been treated for syphilis whilst serving with the Army in Korea but had been discharged cured. The husband almost certainly was reinfected after his return to the British Isles and infected his wife either very late in pregnancy or early in the puerperium.

The interesting features of this case were: (1) The repeatedly negative dark-ground examinations. (2) The histological suspicion that the cervical lesion was a carcinoma.

Argentaffinoma of Ovary.—P. E. HUGHESDON, M.B.

The patient, an obese coloured Jamaican woman of 69, twenty-one years past the menopause, para-15+4, was admitted to U.C.H. complaining principally of right-sided abdominal pain and a painful abdominal lump for six weeks, and attacks of giddiness of a few minutes' duration for a year. She also had nausea, faintness, vomiting, weakness, headaches, watery eyes and difficulty in reading. General examination showed only hypertension (170/100) with normal heart and lungs. The abdomen was obese and the liver was not felt. There was a tender mass of 14 weeks' pregnancy size rising out of the pelvis. Pelvic examination showed a lax vagina, lacerated cervix, a hard mass in the pouch of Douglas and apparent continuity between the abdominal mass and the uterus.

Laparotomy disclosed a coconut-sized right ovarian cyst and a tangerine-sized solid enlargement of the left ovary which had prolapsed into the pouch of Douglas; both were

removed. The uterus, which was small and appeared normal, was left. Convalescence was uneventful, save for a mild urinary tract infection; there was no post-operative vaginal bleeding. As the giddiness, &c., continued she was seen by a physician, and in the ear and eye departments, and nothing of note elicited; she was discharged fairly well.

The 7 blocks made of the right cyst (a typical hair- and tallow-containing unilocular dermoid) showed only skin, respiratory canal—with their associated glands—bone, and marrow; no gut or carcinoid. The left tumour was solid, tough, butter-yellow when first seen, much yellower later (due perhaps to the pigment in these tumours being an artefact of formalin fixation). The 10 blocks made showed only a typical argentaffinoma with mixed adenoid and solid cell masses, the latter recalling a microfolliculoid granulosal tumour. Distinctive features were the frequent presence of a clear marginal cytoplasmic rim, containing brown pigment and giving a rather marked argentaffin reaction, and the often curiously abrupt transitions between the 2 patterns (*see* Figs. 1 and 2). The fibrous stroma was not distinctive; there was both venous and lymphatic permeation.

FIG. 1.

FIG. 2.

FIG. 1.—×157. Fontana's silver and hæmatoxylin. Solid "microfolliculoid" mass, showing black silver granules, especially in cytoplasmic rim.

FIG. 2.—×196. H. and E. Pallisaded small solid and adenoid masses, with characteristic abrupt transition across segment of latter.

The uniformity and solidity of the left tumour make it more likely to have been a metastasis from an intestinal primary than a local development in a teratoma. The patient's attacks of giddiness, &c., may well have been part of the syndrome recently described by Thorson and co-workers (1954) in advanced abdominal carcinoidosis, the flushing, &c., being masked by her colour. The vital feature is probably adequate metastasis outside the portal area which in women tends to involve the ovaries, though this is not usually prominent with this tumour (Ariel, 1939). Unfortunately the patient failed to attend for re-examination.

There are 6 recorded cases of local development of argentaffinoma in a teratoma (Mitchell and Diamond, 1949), though one of these is suspect.

A second case, illustrating this combination, with very similar anatomy to the first, was briefly shown.

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JOINT MEETING No. 3

Section of Psychiatry with Section of Neurology

Chairman—W. MAYER-GROSS, M.D., F.R.C.P.
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The Hippocampal Formation in Temporal Lobe Epilepsy

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LESIONS of the Ammon's horn in epilepsy have been known for more than 125 years, but systematic research into their pathogenesis was not begun before 1927. In this year Spielmeyer published the results of his investigations in which he showed that sclerosis of Ammon's horn is caused by disturbances of the blood circulation and anoxia associated either with major epileptic convulsions or with other anoxic conditions. This line of research has been much elaborated by the school of Spielmeyer and, in relation to epilepsy, by Scholz (1951, 1953). The selective vulnerability of Ammon's horn, and particularly of that part of the pyramidal layer known as Sommer sector, has been explained by peculiarities of the blood supply, by an inherent pathoclisis, or, as Scholz (1953) has recently suggested, by a combination of both vascular and systemic factors.

The year 1927 witnessed an even more important departure. Maximilian Rose (1927) challenged the olfactory theory of Ammon's horn function by demonstrating its independent phylogenetic development, reaching its highest differentiation in the human brain. Rose's claim has been amply confirmed by anatomical work, in this country especially by that of le Gros Clark and his associates (*vide* le Gros Clark and Meyer, 1950). Since then, experimental investigation into the function of the hippocampus has rapidly expanded. The early observations by Papez (1937) and Kluver and Bucy (1939) on changes of emotional behaviour, feeding habits and sexuality after bilateral experimental lesions of the cornu ammonis were followed by interesting electrophysiological work by Maclean, Kaada, Pribram, Delgado and others (for literature *vide* Maclean, 1954; Fulton, 1951; Gastaut, 1953). Ammon's horn is considered by these workers at Yale to be a constituent part of the visceral brain, together with the uncus, amygdaloid nucleus, the anterior insula, posterior orbital and anterior cingular region. Although this experimental work and its interpretation is still in a state of flux, Maclean has developed the view that the frontotemporal portion of the visceral brain is concerned specifically with memories, feelings and actions in relation to the oral senses. Ammon's horn, uncus and amygdaloid nucleus are in close spatial relation with each other as well as with the hippocampal gyrus of which they form a part, and it is the combination of these centres to which the term "hippocampal formation" refers.

There have also been other interpretations of the function of these hippocampal centres. Grünthal (1947) observed bilateral destruction of the Ammon's horn as the only change in a case, aged 67, of severe dementia with oral tendencies which followed hypoglycæmic coma. The author interpreted this finding as evidence that normal function of Ammon's horn is a prerequisite for the highest intellectual performance and for the co-ordination of intellectual with affective behaviour. This thesis has been accepted, in principle at least, by Imhof (1948), Ule (1951, 1954), Glees and Griffiths (1952) and Hegglin (1953). Grünthal's concept of the Ammon's horn serving as an unspecific activator has much in common with Herrick's (1933) and le Gros Clark's (1950) ideas. Quite recently they have also found some experimental support through the work of Green and Arduini (1954) who observed concomitant activity in the hippocampus after stimulation of the activating mechanism in the brain-stem with consequent arousal activity in the neocortex. Again Feindel and Gloor (1954) reported evidence suggesting that the amygdaloid complex, like the reticular formation in the brain-stem and thalamus, is a structure capable of exerting diffuse regulatory effects on other cerebral regions.

This is a very summary review of the historical development of the problem. Almost overnight, what had been mainly a theoretical discussion has become a problem of practical

importance through the introduction of the operation of anterior temporal lobectomy. In 1953, Earle, Baldwin and Penfield published their concept of incisural sclerosis which involves the hippocampal region and the first temporal convolution more consistently than any other part of the temporal lobe. Incisural sclerosis was found by the Montreal workers to be present in 66% of their total material, i.e. in all cases in which the epilepsy was not caused by ordinary focal lesions such as tumour, trauma or inflammatory disease; these workers claimed the lesions to be exclusively due to herniation at birth.

In the same year, Sano and Malamud (1953) published their report on 50 anatomically investigated epileptics, which also aroused much interest. Sano and Malamud found Ammon's horn sclerosis in 29 of 50 cases of unselected epilepsy. After exclusion of unsuitable cases, they established that almost all cases with positive Ammon's horn sclerosis had exhibited some clinical and electroencephalographic evidence of temporal lobe seizures during life. This investigation confirms the results of a similar study by Stauder which was published in 1935, but has curiously not received attention in the recent literature. Stauder found Ammon's horn sclerosis in 36 out of a total of 53 cases; 29 of these cases had shown clinical signs of temporal lobe lesion. On the other hand none of the 17 cases with normal Ammon's horn had shown clinical features of involvement of the temporal lobe.

In our own material—so far—the correlations are not nearly as conclusive. In a recent publication (Meyer, Falconer and Beck, 1954) definite Ammon's horn sclerosis was found in 7 of 12 cases of our second group which is comparable to the "incisural sclerosis" group of Earle, Baldwin and Penfield. This second group has now grown to 20 cases, but again of the 18 cases in which tissue of Ammon's horn was available, sclerosis of a degree comparable to the findings of Sano and Malamud was found in only 12, i.e. in 66%, which is not significantly higher than its average incidence in all types of epilepsy. There are possible explanations for this discrepancy. In some of the 6 cases without Ammon's horn sclerosis, the Ammon's horn, although there was no conspicuous loss of neurones, showed increase of glial cells within considerable parts of the pyramidal layer, a change which might not be without functional significance. There were in these 6 cases also—apart from marginal and white matter gliosis—rather indefinite lesions in other parts of the temporal lobe. It is possible that the epileptogenic focus in these cases may have been situated outside the tissue available for histological investigation. In fact, X-ray findings suggest that the lesions in 2 cases were bilateral and an Ammon's horn sclerosis might well be present in the unoperated hemisphere. It may thus be that ultimately the discrepancy between Stauder's and Sano and Malamud's and our own figures may become smaller.

In addition to the Ammon's horn, we have in our material given attention to the uncus and, in particular, to the *amygdaloid nucleus*. In 4 of the few cases in which tissue was available, there was in the amygdaloid complex of nuclei, focal or diffuse loss of neurones with subsequent gliosis, as is demonstrated in Figs. 1–3[1]. Unfortunately we have—so far

FIG. 1 (*Case* 20).—Nissl stain; ×9·2. Severe nerve cell loss mainly in the uncus and in the ventral part of the basal amygdaloid nucleus.

[1] Illustrations similar to Figs. 1, 4 and 5A but taken from different sections have been included in a contribution by one of us (A. M.) to a Symposium on temporal lobe epilepsy held at Marseilles on November 14–19, 1954, and to be published by Masson et Cie, Paris.

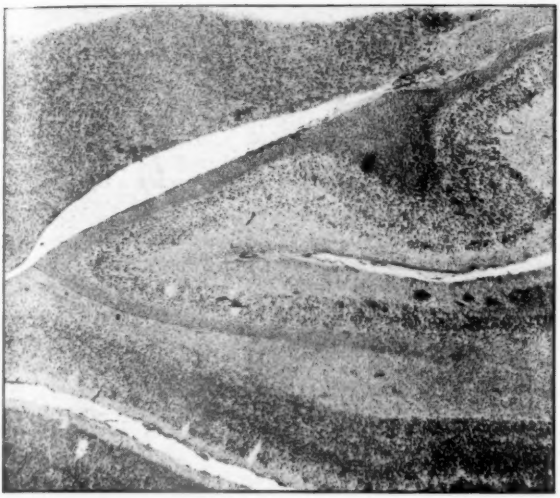

FIG. 2 (*Case* 22).—Nissl stain; ×9·4. Loss of nerve cells and severe white matter gliosis in the uncus. Paucity of nerve cells and glial proliferation in amygdaloid nucleus.

—not obtained successful glial stains (which are known to be difficult in biopsy material) and we were therefore compelled to assess gliosis from the number and appearance of the macroglial and oligodendroglial cells (Fig. 3A and B). It is seen in the photomicrographs that the lesion is more or less confined to the paraventricular region within the basal nucleus which apparently is not concerned with olfactory function and from which, according to Fox (1943) and Adey and Meyer (1952) the stria terminalis arises to convey fibres to the hypothalamus and particularly to the ventromedial nucleus.

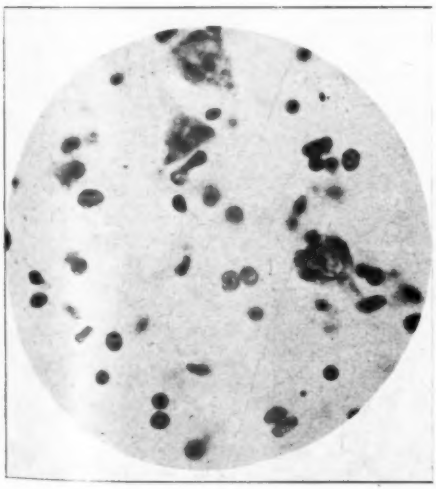

FIG. 3A (*Case* 21).—Nissl stain; ×525. Nerve cell loss and increase of astrocytic nuclei in amygdaloid nucleus.

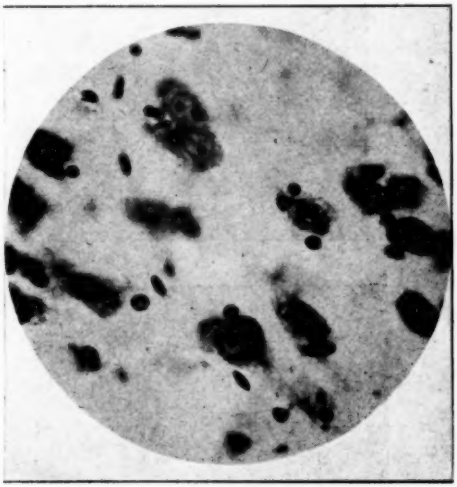

FIG. 3B.—Normal control for comparison.

Since the interpretation of biopsy findings is difficult, it is of interest that we have recently had the opportunity of finding amygdaloid change also in 2 post-mortem cases in which severe and repeated status epilepticus had been a predominant feature. One was a case of a child aged 8 suffering from Still's syndrome, in the course of which repeated epileptic status occurred leading to a state of considerable dementia. The lesions which are described in full in another publication (Meyer, Beck and Shepherd, 1955) were widespread,

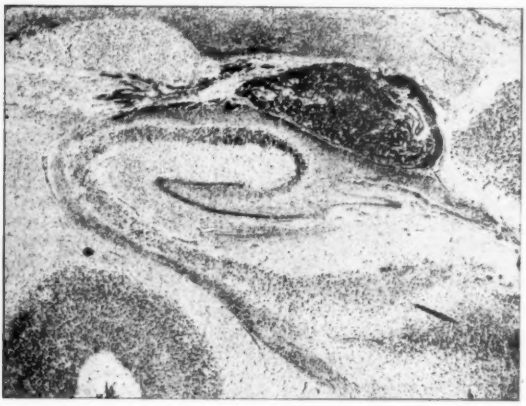

FIG. 4.—Second post-mortem case. Nissl stain; ×9·1. Severe shrinkage of Ammon's horn and nerve cell loss in Sommer sector (h1), end-plate (h3–h5), and fascia dentata. Fibrosis and calcification of choroid plexus.

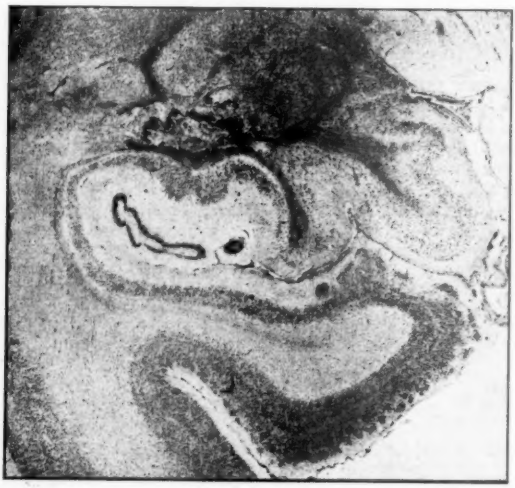

FIG. 5A.—Second post-mortem case. Nissl stain; ×4·9. Severe loss of nerve cells in uncus and amygdaloid nucleus with formation of a glio-mesodermal scar which includes proliferated ependymal cells.

FIG. 5B.—The same in van Gieson stain; ×6·7.

but were most marked in the temporal lobe and in the Sylvian region. The Ammon's horn showed typical selective sclerosis and the amygdaloid nucleus, particularly in its ventral aspects, contained a considerable area of incomplete softening, recognizable on macroscopic inspection. Within the damaged area most of the nerve cells had disappeared.

The second case concerned a patient who had been suffering from recurrent attacks of mania, the last of which had become chronic. A prefrontal leucotomy was performed when she was 43 years old. As was seen at autopsy, the cut had been located in a posterior plane and had resulted in an unusually complete severance of all fibres connecting with the frontal region, including Brodmann's area 6. The caudate nucleus was also damaged on one side. This posterior cut accounts for the severity of the post-operative personality change and for other undesirable sequelæ such as œdema and trophic disturbances which made their appearance about four months after the operation.

Epileptic convulsions began six months after the leucotomy. In the first year these were very numerous and on many occasions severe status epilepticus occurred. Severe major and minor attacks persisted throughout the survival period of seven years. Death occurred suddenly from coronary thrombosis.

At necropsy, apart from the leucotomy lesion, there was slight thickening of the meninges and some shrinkage of both frontal poles. The arteries at the base and elsewhere were free of atheroma or other abnormality. The Ammon's horn was sclerosed on both sides, but more severely on the left than on the right. On the left it was much shrunken (Fig. 4). The Sommer sector (h1) was degenerated with only a few calcified nerve cells persisting. There was total loss of nerve cells in the end plate (h3–h5). Both uncus and amygdaloid nucleus showed considerable loss of nerve cells and extensive glio-mesodermal proliferation (Figs. 5 and 6). In the uncus some of the remaining nerve cells were calcified. The densest

FIG. 6.—Second post-mortem case. Nissl stain; ×5·1. Loss of nerve cells in basal and medial parts of amygdaloid nucleus.

fibrosis was displayed around the anterior cleft-like extremity of the inferior horn with proliferated ependymal cells included in the glio-mesodermal scar. The lesion extended rostrally, affecting mainly the ventro-medial portion of the amygdaloid nucleus (Fig. 6). There was no major lesion in the remaining part of the temporal lobe. The globus pallidus was intact.

To our knowledge, extension of the sclerosis of Ammon's horn into the amygdaloid nucleus, following severe epilepsy or other types of anoxia, has not been reported in the literature. Scholz (1951) in his recent monograph on epilepsy makes no reference to this centre. Only Brockhaus, who published a paper on the amygdaloid nucleus in 1938, described status marmoratus in the amygdaloid nucleus and the striate body in 2 cases of infantile diplegia.

Obviously our observations require confirmation and amplification before it will be possible to assess their significance for the pathology of epilepsy, and of temporal lobe epilepsy in particular. It is of interest to note that recent experimental work by Gastaut (1953) and associates and by Magnus, Ponsen and Rijn (1954), has suggested the amygdaloid nucleus, rather than any other centre of the so-called visceral brain, to be the focus from which psychomotor attacks in animals can be elicited most easily by electrical and chemical stimulation. In the human brain Feindel and Penfield (1954) regard the periamygdaloid region (including the uncus, the amygdaloid nucleus, the ventral claustrum and the insula) as mainly responsible for temporal lobe seizures.

All 6 cases with amygdaloid lesions had suffered from frequent severe convulsions. In 5 of the cases exceptionally severe status had occurred at the onset of the disease. It may be that only in such cases of special severity is an amygdaloid lesion to be expected. This would reduce its general incidence to a relatively small number, but it is possible that this type of case is perhaps more frequent in our material of temporal lobe epilepsy.

In all 6 cases amygdaloid involvement was associated with sclerosis of the Ammon's horn and of the uncus. This simultaneous affection points to a common pathogenesis; in fact, all three centres receive their arterial blood supply from anterior branches of the anterior choroidal artery: they may also have common pathways of venous drainage, although these are less well known. However, to discuss the pathogenic events in detail would lead us into a most intricate and complex problem of selective vulnerability. A full discussion of this and other ætiological problems must be left to a later stage of investigation.

Summary

Recent physiological research concerning Ammon's horn, uncus and the amygdaloid complex and its relation to the pathology of temporal lobe epilepsy is briefly reviewed. The incidence of Ammon's horn sclerosis, which was 66% in the authors' biopsy material, is discussed in the light of figures published by other workers.

In a small number of biopsy and post-mortem cases, Ammon's horn sclerosis was found to combine with a lesion of the amygdaloid nucleus. The significance of this new finding to the pathology of epilepsy cannot yet be assessed.

Acknowledgments

We are greatly indebted to Mr. Murray Falconer, without whose skill it would have been impossible to submit the medial temporal structures to histological analysis.

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Effects of Anterior Cingulectomy in Man[1]

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THE anterior part of the cingulate gyrus (Area 24 of Brodmann), though topographically remote from the hippocampal region which Professor Meyer has discussed, may not be so much functionally separated. Firstly, there is a striking similarity between some of the more marked behaviour changes in monkeys after cingulate excision and Bucy's temporal lobectomy preparations; and secondly an anatomical pathway via hypothalamus and thalamus is established which can provide connexions between hippocampus and cingulate gyrus, and the evidence suggests that this gyrus is the main cortical end-station for such connexions. It may therefore be that so far as function is concerned we are viewing two parts of one mechanism.

When bilateral ablations of the anterior cingulate area are made in monkeys profound changes in behaviour are noted. They affect particularly the sphere of emotional reactions to the environment and have been variously described as increased tameness, loss of aggression and loss of fear and appreciation of danger. They were demonstrated by Smith (1945) and later by Ward (1948), and we were ourselves able to confirm them in 7 animals operated on in collaboration with Dr. Paul Glees in 1949 (Glees *et al.*, 1950). The changes were certainly striking. There was a loss of the normal reaction of fear to both animate and inanimate objects, even to so highly charged a stimulus as the net by which the animals were usually caught, so that behaviour towards man was profoundly changed. What has been termed "social behaviour", the reaction to other monkeys in the group, was also modified. Further, there was a quite unusual brevity and lack of persistence in those reactions of fear and apprehension that could still be elicited. This behavioural change seemed to be linked specifically with the anterior part of the cingulate gyrus because when similar extirpations were made in Area 23 more posteriorly, they were not observed. Indeed, apart from some post-operative malaise there was strikingly little in the way of behaviour change at all. (Glees, 1954.) The observations suggested that if an area with similar functions could be extirpated in man, it might here, too, change the emotional response to the environment.

It was with this in mind that we considered the possibility of limited cortical excisions in this area in man as an alternative to the rather haphazard procedure of leucotomy. Every care was taken to limit the excision to the area shown in Fig. 1. The removal was a subpial

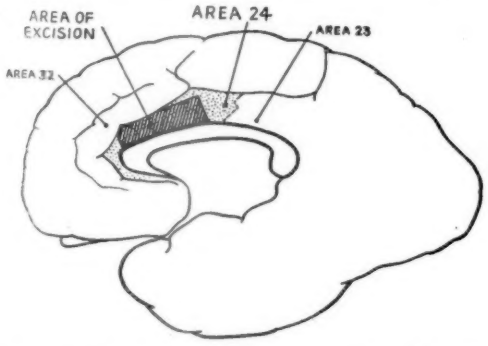

FIG. 1.—Diagram of medial surface of the brain showing area of operative removal in relation to Brodmann's areas.

suction ablation and damage to the branches of the anterior cerebral arteries was avoided—at times a small bridge of tissue being left beneath them to achieve this. The area ablated varied slightly from case to case, but was about 4 cm. long by 1 cm. wide by 1 cm. deep. Since 1948, 35 of our patients have had the operation, and 5 autopsies are now available: 1 directly due to the operation and 4 from causes unconnected. They confirm that we have achieved the small lesion we planned, though in one of them the lesions were placed too high and involved Area 32 on each side. In particular, there was no unintentional damage to the convexities of the hemispheres, and no vascular changes extending deep towards the head of the caudate such as we saw in some of our monkeys, where vessels are admittedly

[1] The observations here reported represent the collaborative work of a group including neurosurgeons, neurologists, physiologists and psychiatrists. The operations were done by the late Sir Hugh Cairns and by Mr. Walpole Lewin. But quite apart from the operative procedure, it was especially Sir Hugh's guidance and encouragement that allowed the work to get started and continue.

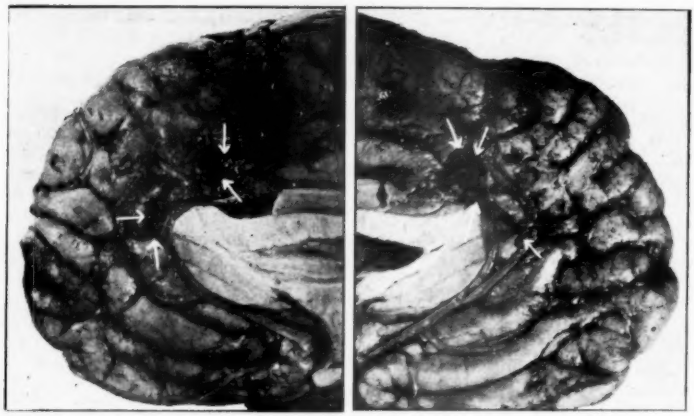

FIG. 2.—Extent of surface lesions on right and left sides in Case I. S.

far more friable. Figs. 2–4 illustrate these points. They are from a patient who died in her sleep some weeks after operation (Case I. S., Table II). She was a severe hypertensive with much myocardial change, though the evidence for recent infarction was not convincing. Fig. 2 shows the extent of the surface lesion brought out more clearly in a drawing of the left side in Fig. 3. Fig. 4 shows the depth of the lesion which has infringed some of the fibres of the cingulum and possibly the corpus callosum. I mention this because the cingulum is probably always injured to some extent in operations on the medial surface of the hemisphere and the possible importance of this tract, especially as a pathway of hippocampal connexion has perhaps been neglected. Both Simpson (1952), using degeneration studies, and more recently Pfuhl (1954), from less reliable fibre dissections, showed a definite contribution to the cingulum from the hippocampus: and the latter found it from the amygdaloid nucleus alsò.

I have emphasized that we do seem to be making limited lesions, because whatever permanent changes occur after operation must presumably be due to alteration of functions mediated in some way by this small area. We have no evidence so far of more extensive frontal lobe involvement either by operative trauma or more widespread vascular change. Indeed, in some of the histological specimens small arterial branches may be seen with the outer coat damaged but still remaining patent and functioning, an observation which emphasizes how robust the human as compared with the monkey's vessels are. These lesions are also smaller than those made by Le Beau (1953) who has now published some 30 cases of operations on the medial aspect of both frontal lobes, but who has deliberately extended his ablations at times to Areas 32, 12 and possibly 25.

When speaking of the regional anatomy of the cortex it is still convenient to use Brodmann's

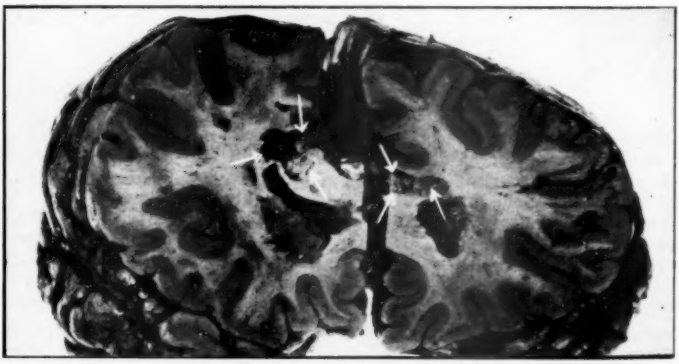

FIG. 4.—Transverse section (at different levels on the two sides) to show depth of lesions in Case I. S.

areas as a topographical lingua franca, and I have done so for this reason. However, their anatomical basis is now questioned and their recognition macroscopically and at operation is inevitably very approximate. I do not wish to imply any unreal accuracy or precision in site of lesions, but would emphasize only that they were small in extent.

Detailed anatomical studies will be published in due course by Dr. Glees, but broadly speaking the efferent connexions of the area in man appear to be similar to those defined earlier in our study of monkeys. In Fig. 5 these are summarized. It may be seen that there

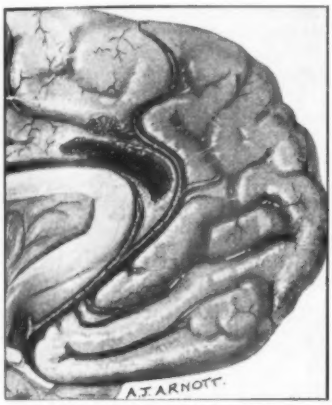

FIG. 3.—Drawing of left side from Fig. 2.

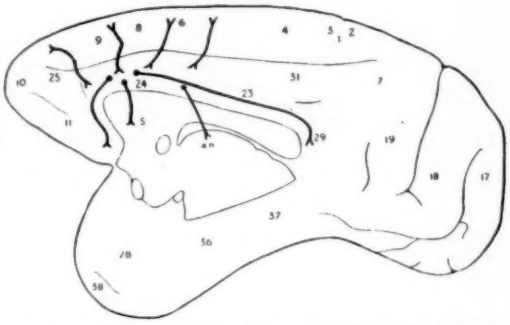

FIG. 5.—Summary of efferent connexions of anterior cingulate region in the monkey. The symbol >—< indicates a two-way connexion. A.N.=Anterior nucleus. S=Septal cortex.

are extensive intracortical connexions, upwards towards the convexity, downwards to the orbital frontal regions and also backward to the more posterior medial Area 29. There are also connexions to the anterior nuclei of the thalamus.

When it was first employed, the operation had to be done only on those patients whose condition justified the use of a procedure which was on trial. During this stage 18 chronic deteriorated cases were treated. The majority were schizophrenics and all were selected as far as possible because they had either marked obsessional features or outbursts of aggression or other conduct abnormality which seemed to be based on an environmental stimulus rather than an internal or hallucinatory one. Diagnoses included 11 schizophrenics, 2 cases of undiagnosed dementias with episodic aggression, 1 paraphrenic, 1 presenile dementia with marked obsessions, 2 melancholics and 1 episodic aggression in post-encephalitis lethargica. 3 died—1 post-operation infection, 1 pneumonia, 1 mesenteric thrombosis. 5 cases had subsequent leucotomies, 2 with marked improvement. 3 had had previous leucotomies with transient or no benefit and 1 of these showed sustained improvement after cingulectomy. Although no permanent clinical benefit resulted in the majority, there was some early change in all of them. During the first few weeks after operation conduct improved to some extent and there was greater accessibility. In the first few days this was sometimes striking. A few cases showed improvement lasting for months, and in 3 it seems to have been permanent These effects may well have been only partially due to the operation, but they were sufficient, combined with a reduction in the seemingly provoked aggressive outburst and obsessional thought and behaviour, to encourage us to pursue the matter. The results also made it clear that the sometimes catastrophic personality changes occasionally seen in posterior leucotomies did not occur. Indeed, in those few cases where it was possible to judge, the changes usually associated with frontal lobe dysfunction appeared to be present only in minor degree. We therefore felt it justified to try the procedure in cases of disabling mental illness with well-preserved personalities who had failed to respond to other measures and whose prognosis was considered bad.

The cases that were now considered were brought forward because basic personality was well preserved and the intellectual and social setting of the patient was such that deterioration in standards of personal behaviour was especially likely to be a disadvantage. Within this group we selected as far as possible those whose illness involved excessive emotional reaction to the environment—anxieties rather than depressions—and those with obsessive symptoms, both the single obsessional idea with its aura of compulsive protective ritual and the more

diffuse obsessive ruminations. 17 such patients have now been operated on. Diagnoses, which usually represent the consensus of opinion of five psychiatrists, are stated according to the predominant clinical feature of each case. In most cases other features were also present, e.g. obsessions with anxiety, depression with obsessional symptoms, &c. In a few, the prominence of these other features almost matched that of the diagnostic label. All cases without exception also showed some degree of increased tension. Table I shows the details of 7 mainly affective disorders.

TABLE I.—7 UNDETERIORATED CASES WITH AFFECTIVE DISORDERS.

Case	Age	Sex	Diagnosis	Length of illness (years)	Length of F.U. (years)	Result
R. B.	44	M	Anxiety	6	4	Improved*
M. W.	29	F	Anxiety	3	3	Greatly improved
J. G.	44	M	Anxiety	5	2	Improved
F. L.	54	M	Anx./Dep.	4	3	Improved. R.
A. M.	48	F	Depression	20	10/12	Unchanged. L.
M. We.	43	F	Anxiety	10	1½	Greatly improved. D.
P. A.	37	M	Anxiety	3	3	Improved. R.

* Anxiety and obsessional symptoms cleared entirely, but aggressive and mildly paranoid reaction developed.

R, Relapsed; details in text. L, Leucotomy done 10/12 later. D, Died of hypertensive heart disease.

Of this group, 4 were improved—they were happier, able to live at home, to return to work of sorts and to get by with occasional out-patient psychiatric treatment only, though their symptoms were still present and limited their activities. 2 were greatly improved—their symptoms were to all intents and purposes abolished and they were able to lead full normal lives. They regarded themselves, and were regarded by their relatives, as cured. In fact I would myself have used this word to describe some patients in this group, but my psychiatric colleagues felt it was too bold for an illness which might have been involving the patient's personality for decades with possibly prolonged cycles of remission and relapse. One was unchanged, and had a leucotomy later with some permanent improvement. One case (R. B.) classed as improved showed a rather interesting development of a mildly paranoid reaction. Much of his time before operation was devoted to worrying over trivial matters and in an excessive meticulousness in performing all he did to the highest possible standard. After operation these symptoms cleared and his energy was expended with less care and circumspection on slightly aggressive salesmanship. When this brought him into conflict with his superiors he complained that they were against him. A careful investigation revealed that there was some slight justification for this view, but not as much as he thought. A change of job to salesmanship of a simpler type allowed him to adjust better, though he remained bitter and hostile about his previous employers. A further case, F. L., also in the improved group, maintained his improvement for some two and a half years and then relapsed. But the features of his second illness differed from the first. Whereas before he showed marked tension and anxiety with many obsessional features, he later had a much more flat depression and obsessional symptoms were not prominent.

Another case, P. A., also showed a marked reduction in tension and anxiety and obsessive hypochondriacal complaints about his bowels, and was able to return home for a short while. However, nine months later he began to show bizarre delusions about the decay of his body and was readmitted to hospital where a diagnosis of schizophrenia was finally made. Now, three years after operation, he is slow and apathetic with persistent delusions, but no evidence of anxiety or tension.

Among the 10 mainly obsessional patients shown in Table II, 6 were greatly improved

TABLE II.—10 UNDETERIORATED CASES WITH PREDOMINANTLY OBSESSIVE SYMPTOMS

Case	Age	Sex	Diagnosis	Length of illness (years)	Length of F.U. (years)	Result
J. F. H.	27	M	Obs.	8	1	Greatly improved
D. S.	35	M	Obs.	5	6	Greatly improved
M. D.	42	M	Obs./rum.	9	3	Improved
F. E.	41	F	Obs./rum.	3	4	Greatly improved
K. S.	38	F	Obs.	20	6	Greatly improved
I. S.	42	F	Obs.	25	2/12	Improved. D.
A. A.	51	M	Obs./rum.	20	4	Greatly improved
J. M.	27	F	Obs.	8	3	Improved*
D. C.	31	F	Obs.	6	5/12	Improved
J. R.	62	M	Obs.	4	3	Greatly improved

* Relation of improvement to operation doubtful.

D, Died, probably coronary disease.

and 4 improved. However, in one of the latter the part played by the operation was not certain. This patient (J. M.) had previously had a leucotomy—the only one in this group of well-preserved cases—with transient benefit for four months. Following the cingulectomy her disabling obsessions and rituals cleared to some extent but she appeared to be relapsing once more when she struck up an intense friendship with a slightly younger woman of considerably greater intelligence, who was also for a time under psychiatric treatment. Following this, improvement was rapid and the two seemed to help each other in losing their symptoms and living a full and normal social life. When last seen she was still maintaining this friendship and it was questionable how she would fare if it was interrupted.

Apart from the therapeutic assessment, the general behaviour changes noted in these patients post-operatively are of some interest. In the early days they showed undoubted evidence of the kind of behaviour seen in frontal lobe dysfunction. They were uninhibited, overtalkative, tactless and easily distractable; expressing their feelings and using expletives freely. But these symptoms were not marked and had largely cleared after a week or so. Fears and obsessions were not suddenly abolished, but faded out gradually over weeks or months. However, tension and marked emotional reaction to these symptoms were certainly reduced immediately after operation. Amongst more permanent sequelæ was a slight reduction of inhibition. They would say what they thought more readily and do what they wanted with less thought about it. These changes were not obvious and did not interfere in any way with social or family life. Indeed, they were regarded by relatives as a return to normal. There was also an undoubted reduction in the tendency for thoughts and emotions to persist and become obsessive. If they were annoyed or worried they expressed their feelings and the matter was ended. *Pari passu* with this was a slight loss of drive and concentration and perhaps of depth and range of general interests; but also some increase in their ability to make social contacts, since their emotional reactions though more short-lived were also more readily elicited. Though no increase in sleep was noted, complaints of tiredness were common in the first few months. These changes illustrate well the point that Elithorn (1955) made recently that one cannot really separate therapeutic effect and personality change. What emerges clearly is that in none of these cases were the personality changes a disability or disadvantage to the patient. None was made worse by the operation. The changes were not obvious even to near relatives, and when noted were regarded as signs of cure.

It is worth emphasizing also that this assessment has been continued for some years in the majority of cases, and that with the experience of early and later reports on leucotomy in mind, we looked especially in the home and work situation for the later emergence of adverse personality changes and found no evidence of this.

The changes that do occur may be summarized as a reduction of inhibition and a loss of perseveration in both cognitive and emotional spheres.

The operation is a major neurosurgical procedure, and its advantages must be weighed against those of other more simple interventions. It certainly produces less blunting of personality than leucotomy and probably less than orbital undercutting, though the difference here is less marked. It has to be considered for the well-preserved patient of potentially high intellectual and social status, disabled by obsessional or severe anxiety neurosis; and on present results we feel it should be considered seriously.

Leaving the interesting but difficult field of personality changes, two further points of more strictly neurological interest arise. First, the question of epilepsy. Le Beau (1952) has used a bilateral ablation of Area 24 and near-by areas in the treatment of cases of conduct disorder with episodic aggression and often overt epilepsy, and has reported improvement in 16 of 23 cases. Of our 35 cases, 4 had epilepsy before operation. In 3 this consisted of rare isolated fits, in 2 only in childhood, but in 1 the picture was similar to Le Beau's cases—a severe episodic aggression with epilepsy and some suggestion of dementia. This case showed an undoubted reduction in her fits and some reduction of her aggressive outbursts. The other 3 had a recurrence of their fits, which they had not had for years, in the first post-operative week, and in one this proceeded to status epilepticus. Later on, in 1 of the 3, fits persisted as an occasional attack despite anticonvulsants, while in 2 there were no further fits and anticonvulsants were abandoned after four to six months. In a further 3 cases with no history of fits, *grand mal* attacks occurred in the first few post-operative days, but in further periods of from six months to six years, there have been no more fits. Only 1 of our cases, M. D., with no evidence of pre-operative epilepsy has had persistent attacks. These did not start until three months after operation, and it is interesting and possibly significant that they are of the inhibitory or akinetic type. The occurrence of fits in the immediate post-operative period, especially in frontal lobe surgery, is of little significance so that these observations do not necessarily conflict with Le Beau's.

Secondly, the more physiological functions of this area. Animal work has suggested that the anterior cingulate has both autonomic (Smith, 1945; Ward, 1948) and suppressor

functions (McCullough, 1949). We had the opportunity of stimulating the area in 6 patients operated on under local anæsthetic. The stimulator with non-polarizable electrodes delivered a square-topped wave, pulse duration was varied from 5–20 millisecs., current from 2–3·5 milliamps., frequency from 20–50 c.p.s. and stimulus duration 5–10 secs. Responses were disappointingly negative. During stimulation patients counted and were asked to recall some past event to test memory functions. Both these activities were carried out uninterruptedly throughout stimulation. Voluntary movement of hands and feet was also carried out. In 4 cases when stimulating anteriorly just in front of the genu of the corpus callosum momentary arrest or change of respiratory rhythm occurred and was noted by the patient, but this could not be elicited consistently. In 2 cases also an epigastric sensation was noticed and described as "fluttering" or "sickly feeling", and in one patient this was reproduced several times when using 3·5 milliamps. These responses were not due to accidental stimulation of dura or falx: stimulation of these structures in the conscious patients gives quite a different response.

As extirpation of the gyrus was being done, in 3 cases visceral or vasomotor changes occurred. In all of them this was during removal of the second side. In 1 the change consisted of sweating, sudden drop in blood pressure, an unpleasant epigastric sensation and then vomiting. In 1 it was an intense unpleasant epigastric sensation—a similar less intense sensation had also been elicited on stimulation in this case. And in 1 sweating was accompanied by sudden involuntary evacuation of bladder and bowels. This patient was aware of the occurrence and expressed distress and shame about it.

The significance of these findings must depend to a large extent on whether such changes occur during extirpation of other areas under similar conditions. The experience of traumatic brain surgery—not perhaps strictly comparable—suggests that they do not.

Visceral and vasomotor changes were specially looked for as a prolonged sequel to operation. During the first few days after operation all patients without exception were occasionally incontinent of urine. This can be contrasted with the observation of the Ward Sister on a busy neurosurgical ward that in the conscious patient who was not incontinent before operation it was unusual to get any post-operative incontinence. However, this symptom usually cleared within a week or so, though some urgency occasionally persisted. In a group of 20 patients blood pressure and pulse-rates were recorded twice daily under standard conditions, for three months before operation and again for three months after. During the first two or three weeks after operation there was a significant lowering of blood pressure, but by one month the change was not significant. Pulse-rate also showed a tendency to drop, but was not statistically significant. In 5 cases the blood pressure and pulse-rate response to adrenaline and Mecholyl was tried (Funkenstein *et al.*, 1949). The tests were done on three occasions before and after operation. No changes were noted except that the post-operative response to adrenaline was less marked and less prolonged. However, the range of normal response was such that the significance of this change was doubtful: though it was felt that further investigation of this type of test, where autonomic response to stress rather than a base-line of function was measured, might be rewarding. In 2 cases, both young deteriorating schizophrenics, although pulse-rate was 70–80 when taken twice daily by the doctor in charge of their ward, whenever I visited and examined them the pulse was constantly very rapid, about 120–130, the heart beat was heaving, hæmic murmurs were present and there was marked sweating of the hands. The visit was a break in their usual routine which required them to come in from the day room to their beds, and occurred weekly for two months before operation. It was thus a slightly unusual stimulus and perhaps a cause for apprehension. After operation, the pulse at my examination was always 70–80, heart action was quiet and the hands dry. Permanent autonomic changes in these cases, however, are insignificant, and if present seem a change in range of response to stimuli rather than a change in base-line.

Several patients also showed an ill-defined change in facial appearance that made them look younger. The majority put on weight after operation—in 4 cases this was very marked —over 28 lb. in four to six weeks. Both these physiological changes are also seen at times after leucotomy. Neither their mechanism nor significance is clear.

Summary

Small bilateral lesions in the anterior cingulate region in man have produced on the psychological side a slight loss of inhibition and a reduction in tension and in the persistence of emotional and cognitive activity. These changes have proved beneficial in patients with obsessional and anxiety neuroses. On the physiological side, both stimulating and excising these areas in the conscious patient have produced little positive effect. Although what changes there are have been in visceral and vasomotor function, the limited evidence so ar

obtained does not seem to warrant assigning specific autonomic functions to this cortex in man.

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A Special Method of Stereotactic Brain Operation

By R. HASSLER, M.D., and T. RIECHERT, M.D.

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IN order to eliminate specific deep brain structures without injury of neighbouring structures for therapeutic purposes, we have constructed an apparatus (T. Riechert and M. Wolff) with the help of which such operations can be performed. It has thus been made possible to reach any point marked in the X-ray picture. With the same needle one can stimulate at the chosen point, record the brain potentials from it and coagulate the tissue around it. The apparatus consists of a base-ring fixed by thorn-holders on the head of the patient. On this base-ring is placed the aiming bow, which carries in a special holder the coagulation needle (Fig. 1). After the base-ring has been fixed an X-ray picture is taken. In this picture we mark

FIG. 1.—Base-ring with aiming-bow and needle-holder fixed to the patient's head.

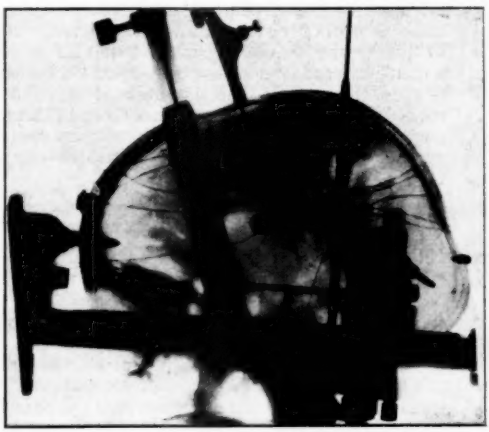

FIG. 2.—X-ray picture of skull with apparatus, including needle in position.

the point to be reached, and measure the distances of the point from the base-ring. Mistakes due to enlargement by the roentgenograms are eliminated. Instead to calculate the angles of the aiming-bow to reach the point, we use a separate phantom-base-ring corresponding in all proportions with the base-ring fixed on the patient's head. The point to be reached in the brain of the patient is marked by means of three co-ordinates on the phantom-base-ring. The aiming-bow is first fixed on the phantom-base-ring and without changing the angles of the needle-holder is then transferred on to the base-ring fixed on the patient's head. The needle is introduced through a burr-hole. The position of the needle-point is controlled by roentgenograms (Fig. 2) by repeated stimulation and by recording the brain potentials at the special point. If the position is correct, coagulation can be performed.

We have so far performed up to 155 of these operations for different indications.

In the following paragraphs some indications are described which were demonstrated in the film. It is necessary to perform an air encephalogram for determination of the individual point of the brain to be attacked. For comparison between the patient's and the phantom brain the distance from intraventricular foramen to the commissura habenularum is particularly important. This we call the ventricle length of the thalamus.

Hyperkinetic movements.—This is an important indication of the treatment. Hyperkinetic movements are due to release of an extrapyramidal neuron system from the regulating influence of the next higher extrapyramidal nucleus. The released nucleus in these cases is the inner segment of the pallidum. The latter is connected by two different afferent pathways with the interior parts of the oral ventral nucleus and with the oral pole of the lateral nuclear complex of the thalamus. Through this system pathological impulses run to the premotor cortical areas in many cases of hyperkinetic disorders. Instead of interrupting the conducting mechanism of the hyperkinetic movements in the precentral cortex which would result in hemiparesis, it was suggested to interrupt the conducting mechanism in the inner segment of the pallidum or in the oral ventral nuclei of the thalamus supplied by the pallidum. This hypothesis proved correct in coagulations performed in a number of patients. A hemiparesis was avoided by this procedure.

Because it is difficult to coagulate completely the structures in question, additional interventions on the spinal cord and its roots were performed with satisfactory effect, especially in some patients with torticollis.

Parkinsonism.—Since the pyramidal tract has a facilitating effect on the rhythm of the tremor at rest originating from the internuncial cells of the spinal cord (Jung) the pyramidal tracts are interrupted at different places for relief of the tremor according to different authors (removal of the precentral cortex by Bucy, pyramidotomy by Putnam, and division of the inner capsule by Browder). These methods had as their result the development of a hemiparesis varying in severity if the tremor was improved.

If one supposes that the facilitating influence of the pyramidal tract also comes through its afferent pathway, coagulations in the thalamic nuclei which project towards the precentral cortex could be of remedial value. In fact, by stimulating these structures we observed an influence on the rhythm of the tremor. Coagulations performed accordingly resulted in improvement of the tremor and disappearance of the rigidity. The first patient operated upon in this manner has now remained well for three years; tremor persists on one side, but in a much reduced degree, and only when the patient gets excited. After bilateral coagulations of these nuclei the connecting fibres to the frontal lobes are also cut as well as those to the medial thalamic nuclei which pass through these nuclei. Therefore in our first patient with parkinsonism a frontal lobe syndrome was seen. In the patients operated on later this was avoided by applying unilateral coagulation only.

Psychosurgery.—In cases with chronic deteriorating psychosis coagulations of the medial nucleus of the thalamus were performed according to the method used by Spiegel and Wycis. The coagulations must not be too restricted to have a therapeutical effect. On the other hand, frontal lobe symptoms can be observed after such more extensive coagulations. The special effects have already been described in an earlier communication.[1]

Intractable pain.—From the two possibilities for treatment of severe pain, we have used the psychosurgical approach (frontal leucotomy) only in exceptional cases because of the personality defects following these operations.

The second method is an attempt to interrupt the pain-conducting pathways in different places. By means of stereotactic operation it is possible to divide these pathways in the thalamus where the pain impulses pass the basal part of the caudal ventral nucleus. Coagulation of this nucleus results in relief from pain without any psychic changes. Before coagulation stimulation with higher frequencies of thyratron currents produces the typical neuralgic pains or painful paræsthesias. By these stimulations the somatotopic representation of the different regions can be demonstrated. The results have been satisfactory in patients with severe facial pain, especially after herpes zoster. All these patients had been treated before by other operations without the stereotactic method.

The method of stereotactic operations promises many new possibilities in treatment of various disorders of the central nervous system; however, much more experience is needed before one can come to definite conclusions as to its value as an aid in precisely locating a lesion.

The method and results were illustrated by a film demonstration.

[1]*See* HASSLER, R., and RIECHERT, T. (1954) *Nervenarzt.*, **25**, 441.

BOOK REVIEWS

The Royal Society of Medicine. The Realization of an Ideal. Written at the request of the President and Council by Maurice Davidson, M.A., D.M.Oxon., F.R.C.P.Lond. (Pp. 201; 29 illustrations. 21s.) London: Royal Society of Medicine. 1955.

In 1805 the Medico-Chirurgical Society was founded as an off-shoot from the Medical Society of London. After a feeble start the new venture grew into a flourishing society which continued to need larger premises as its activities increased. Its centenary year was celebrated by the publication of its history, written by Sir Norman Moore and Mr. Stephen Paget. In 1907 the Medico-Chirurgical Society united with fourteen other medical societies to form the Royal Society of Medicine which was given a new Charter of Incorporation. Since that date the Society has acquired new and larger premises, and its work and influence have developed so rapidly that, to celebrate the 150th year of its existence, it has been thought wise to publish a volume bringing its history up to date. By choosing Dr. Maurice Davidson to write this volume the President and Council made certain that the story would be told in a plain, pure and pleasant literary style, and that it would be imbued with a fine spirit of philosophy. No one can read this volume without gaining a wider and deeper view of the aims and purpose of the Society, and of medicine in general.

As was to be expected, most of the two hundred pages are devoted to the stirring events of the past fifty years. So much has happened during that time that it would need a much bigger book to do full justice to the theme. Nevertheless, Dr. Davidson has given us a clear bird's-eye view of the course along which the Society has progressed. He devotes special chapters to describe the scientific business of the Society, the formation of the Library, the development of the Photographic Department, and the growth of the *Proceedings*.

The Society has been fortunate in the Secretaries who have guided its administration. Well-merited tribute is here paid to the remarkable part played by the late Sir John MacAlister in bringing about the union of the many separate societies, and in helping to overcome the many difficulties which arose in the early days after union. Tribute is also due to the ability and enterprise of Mr. Geoffrey Edwards who helped so successfully to maintain and extend the usefulness of the Society during a critical period of twenty-five years.

A most attractive section, beautifully illustrated by many excellent photographs, is the chapter giving short accounts of those who have occupied the Presidential Chair since the new Charter was granted.

The final chapter, in which the author discusses the part which the Society should play in the field of medical education, is inspired by a healthy but sober idealism. A plea is made that the Society should be ready to expand in new directions, which would at one time have been considered outside its own special sphere. There is here room for difference of opinion and certainly food for thought.

We trust that every Fellow of the Society will hasten to possess a copy of this interesting volume.

Peripheral Vascular Diseases. By Edgar V. Allen, B.S., M.A., M.D., F.A.C.P., Nelson W. Barker, B.A., M.D., M.S., F.A.C.P., and Edgar A. Hines, Jr., B.S., M.A., M.D., M.S., F.A.C.P. 2nd edition. (Pp. xiii + 825; 316 illustrations, 7 in colour. 91s.) Philadelphia and London: W. B. Saunders Company. 1955.

Dr. George Brown of the Mayo Clinic was a pioneer in the study of peripheral vascular disease and this book is dedicated to his memory by his colleagues and pupils. Before Brown's untimely death in 1935, one of the authors, Dr. Edgar V. Allen, had already joined him in contributing to our knowledge of this specialty, and it is fitting that he should lead among the authors of the present work.

That the subject should be regarded as a specialty is a natural claim of this book which deals with disease of all blood and lymph vessels outside the heart with the exclusion of the coronary arteries and of hypertension, although a chapter is devoted to hypertensive ischaemic ulcers of the leg. Coarctation of the aorta and aortic aneurysm are the only clinical conditions that do not appear to fall naturally within the compass of this work, although they each conform with the definition just given to peripheral vascular disease.

The book has 27 chapters, and every subject is described along orthodox lines. Thus, the historical aspect is first chronicled, and this is followed by an account of its pathogenesis and/or pathology, clinical features, special methods of investigation, differential diagnosis, and medical and surgical treatment.

The text which is beautifully illustrated, includes a description of Raynaud disease, scleroderma, erythromelalgia, scalenus anticus, syndrome, arterial embolism and thrombosis, atherosclerosis, periarteritis nodosa, localized and generalized arteritis, arteriovenous fistula, and diseases affecting the venous and lymphatic systems.

The book appears to be faultless, for its writing has been perfectly planned and executed, and the authors deserve the warmest praise for making available to the profession this outstanding work in a section of medicine which has received too little attention in the past. In the meantime, this book has no equal, and it should be in the possession of everyone interested in the diagnosis and treatment of cardiovascular disease.

A History of Medicine. By Ralph H. Major, M.D. (Pp. 1155, 2 vols.; illustrated. £5 5s.) Oxford: Blackwell Scientific Publications. 1954.

The history of medicine is like a long river with many tributary streams; in the upper reaches the main stream meanders slowly and almost aimlessly along, but lower down it receives many smaller streams and flows much more quickly. The historian of medicine must follow the main stream if he wishes to give a connected and readable account, and the minor tributary sources are therefore apt to be neglected. In this well-produced history Dr. Ralph Major has overcome this difficulty by adding to each main section a series of short biographies of those minor but yet sometimes important persons who might otherwise have been overlooked. The result is that these two handy volumes give a complete picture of the growth of medicine from prehistoric times down to the present day. The first volume takes us from primitive times down to the Renaissance and the seventeenth century; the second continues the story to the present time. The style is clear, concise and readable and wise judgment is shown in preserving due balance between the various sections. Though the author states that the book has been written primarily for medical students and practitioners we are sure that all medical historians will find much that is interesting and new, and we believe that this history will immediately take its place as a textbook and a useful book of reference.

There are over four hundred illustrations which help to explain the text; most are good but a few might with advantage be replaced by better reproductions, e.g. the portraits of Oliver Wendell Holmes and of Florence Nightingale. There is a good index both of names and subjects, and a useful bibliography. We only noted one misprinted date, at the bottom of page 175. Altogether a book to be recommended.

The Civilian Health and Medical Services (History of the Second World War, United Kingdom Medical Series). Edited by Sir Arthur Salusbury MacNalty, K.C.B., M.A., M.D., F.R.C.P., F.R.C.S. Vol. 2. (Pp. xi + 406. 45s.) London: Her Majesty's Stationery Office. 1955.

This, the second volume of the history of "Civilian Health and Medical Services" during the Second World War, deals with the Public Health in Scotland and in Northern Ireland, gives a succinct account of the Medical Services of the Ministry of Pensions, and describes the impact of the War upon the medical services in the British Colonies—Hong Kong, Malaya, North Borneo, British Somaliland, Palestine, Cyprus, Gibraltar and Ceylon. The volume is produced in the excellent style which characterizes all the volumes of this great history. Needless to say it is well edited.

The experiences of the Health Services in Scotland and Northern Ireland followed the same, or almost the same, pattern as in England; in Northern Ireland it was slightly modified by the fact that National Health Insurance came under the administration of the Ministry of Labour. The account of the medical services of the Ministry of Pensions is full of useful facts but is curiously impersonal. One looks in vain to see who was in charge of the various departments.

In the section dealing with the Colonies there is much restrained but significant writing. We note that in Malta in 1942 the nutritive value of the diet came down to 1,514 calories for adult men and 1,365 calories for women and children. In Hong Kong in that same year the ration was only 8½ oz. of rice, with a small portion of water buffalo, no vegetables, and rarely any salt or oil. The treatment given to the interned in North Borneo and Malaya, even to those who were sick, makes very unpleasant reading. In North Borneo mental patients were "turned adrift and left to fend for themselves, with the result that few survived". Lepers were badly treated and "finally the whole community was transhipped to Boaan Peninsula, dumped in a coconut plantation and left to manage as best they could". In some instances medical officers were brutally treated and one feels that there is much that could not be written. The work done by our medical officers and nurses under most dispiriting conditions deserves the highest praise, and we would recommend those who

may not have the time to read all through this volume to spare at least time enough to read pages 93 to 110 giving an account of the conditions in Singapore during the Japanese occupation. Heroic work under appalling conditions.

Hypothyroidism: An Essay on Modern Medicine. By Paul Starr, M.D., F.A.C.P. (Pp. x + 127; 25 illustrations. 27s. 6d.) Oxford: Blackwell Scientific Publications. 1954.

This is yet another of the Thomas American Lecture Series and the production of the book is of the usual high standard. It contains material gathered together by the authors from the Thyroid Clinics of the University of Southern California and the Los Angeles County Hospital. The author opens with the observation that hypothyroidism is a disease without clinical history and therefore it behoves the clinician to search it out. This Dr. Starr does with considerable zest and in doing so perhaps relies too heavily on the value of protein-bound iodine levels in the blood of his patients. This involves him in criticism of the usual techniques of assessing the value of laboratory data in the light of clinical symptoms and signs. The basic problem stretches far beyond the field of hypothyroidism, being that of diagnosing chronic disease at what are at present regarded as subclinical levels. We find in the concluding paragraphs that "the citizen being damaged by hypothyroidism does not know. He is not likely to be a doctor's patient".

An uncritical account is given of various methods available for determining the protein-bound iodine and the rest of the book is largely concerned with its application. The reader might indeed question some of the conclusions to which it leads. A further point of interest is the support of the view that "somatic hyperthyroidism" is an entity in spite of considerable criticism from others who have experience in this field. It is difficult nevertheless to get a clear picture of the author's precise view on this subject. One of the chief values of the book is the collection of data it contains on the behaviour of the protein-bound iodine under various conditions and it broadly reflects modern views on the subject. A little space is given to other aspects of hypothyroidism.

Modern Occupational Medicine. Edited by A. J. Fleming, M.Sc., M.D., and C. A. D'Alonzo, M.D., F.A.C.P. (Pp. 414; 44 illustrations, 1 in colour. 75s.) London: Henry Kimpton. 1954.

This is a fresh approach to the subject of industrial medicine. It is not an ordinary textbook, but is rather a symposium compiled by a team of experts. The 30 chapters were contributed by 20 full-time members, including the editors, of the staff of E. I. du Pont de Nemours and Company; 16 of them work in one or more of the medical departments of the Company and many had previously acquired extensive training and experience in industrial medicine; the 4 non-medical contributors were closely associated with the medical departments. There are 7 sections. (1) Organization: includes the evaluation of medical services; administration, with details on personnel, layout, and equipment; physical examinations and records. (2) Prevention: research and toxicological methods, protective clothing, including details of the "Chem-proof air suit"; the function of the industrial hygiene laboratory; and immunizations in industry. (3) Physical environment: temperature, humidity, noise, radiological hazards, and fatigue. (4) Chapters on special topics: medico-legal aspects of occupational medicine, rehabilitation, surgical considerations in industry; canteen management; nursing services; sanitation; and safety. (5) Psychiatry applied to industry, and discipline in relation to mental health. (6) Toxicology: chemical health hazards; many substances and their modes of action are discussed; special chapters on insecticides; the carotid sinus and chemicals which affect it; and tetraethyl lead. (7) This final section deals with the problem of acute poisoning, in the factory, or among the neighbouring general population who may urgently need help.

The emphasis throughout the book is on hazards in the chemical industry and the relationship between these and the physical and mental state of the workers. Much attention is given to assessment of fitness of the "well man" and the selection of suitable occupations of those showing any deviation from the standards indicated by tests and experience and by follow-up observation; for example, the chapter on "preventive medicine in industry" includes studies on factors which may act as stresses, and on physiological change, deterioration and recovery in the presence of stress, and the signs and symptoms of these states, including statistical data for trends in pulse-rate and blood pressure under various environmental conditions and exposures.

The standard set for the practice of occupational medicine as outlined in this book is high, and it may not be possible to implement it fully in the ordinary run of industrial establishments, but there is much that is applicable in every range of work relations and it can be recommended for study by industrial medical officers and all who are responsible for the health, safety and welfare of industrial workers. There are useful references to the literature and there is an excellent index.

Bedside Diagnosis. By Charles Seward, M.D., F.R.C.P.Edin. 3rd edition. (Pp. xx + 408; illustrated. 18s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1955

The popularity of this book has called for a third edition. Most of the commoner aspects of internal medicine are covered, each chapter being devoted to a particular symptom. The style is informal and perhaps "Bedside Companion" would be an appropriate alternative title. The book is useful in jogging one's memory upon many facts which one should know, but which have been forgotten.

Surgery of the Adrenal Glands. By William Wallace Scott, M.D., Ph.D., and Perry B. Hudson, M.D. (Pp. xiv + 150; 35 illustrations. 25s.) Oxford: Blackwell Scientific Publications. 1954.

The word lecture in the publisher's description is well chosen as the authors' purpose is to illustrate a theme rather than to present critical data on which new conclusions can be drawn. However, the book must be received as one of the more important contributions on treatment of adrenal disorder, especially as it comes from the Johns Hopkins School. It has obviously been possible to maintain a close liaison between surgeons and physicians and due acknowledgment is given to Drs. John Eager Howard and Lawson Wilkins for the part they have played in making the book possible. It is most important that the surgeon should be well informed on the function of those parts of the body in which he operates and this aspect of the subject is given due space and is well presented. It is a pleasure to note that Dwight Ingle's view that adrenal physiology is tending to suffer from over-simplification has been given attention. By far the largest portion of the book deals with tumours of the adrenal cortex and medulla, the authors adopting the functional classification to describe these. The text appears to be accurate and complete in the discussion of these lesions. Some reference is made to hyperplastic adrenal cortices in Cushing's syndrome, and the treatment by subtotal adrenalectomy discussed, although the authors appear to have had little experience of this. Diagnosis and treatment of the hormonal and non-hormonal medullary tumours are well reviewed. The standard of the illustrations throughout this section of the book could hardly be excelled. Details of paracoccygeal air-insufflation are given and its limitations, particularly with medullary tumours, indicated. It is most interesting to note that atrophy of the contralateral adrenal is found when tumours causing Cushing's syndrome are removed, but not when virilizing or feminizing tumours are encountered. This is a valuable clinical confirmation of the experimental findings that it is the adrenal cortical corticoids which suppress ACTH secretion by the pituitary. The importance of deciding on the surgical approach according to the merits of the case is considered but there is unfortunately a lack of extensive critical discussion of this subject. Technical details are avoided. Hormonal treatment in the operative phase of both medullary and cortical tumours is discussed and the importance of co-operation with the physician stressed. The book closes with a brief review of the use of adrenalectomy in prostatic and mammary cancer. The authors agree that pain due to secondaries may be alleviated in prostatic cases. They wisely defer judgment of mammary cancer. They therefore are to be congratulated on the excellence and balance throughout. It will also be apparent that the book is equally as valuable to the post-graduate physician as to his surgical colleague.

Neurology. By S. A. Kinnier Wilson, M.A., M.D., D.Sc., F.R.C.P. Edited by A. Ninian Bruce, F.R.C.P.Ed., D.Sc., M.D., F.R.S.Ed., Lt.-Col. R.A.M.C. 2nd edition. (3 vols.; illustrated. £10 10s. per set; £3 10s. per volume.) London: Butterworth & Co. (Publishers) Ltd. Vols. 1 and 2, 1954; Vol. 3, 1955.

Even the most exhaustive textbook of medicine must be completed by its author within a certain period of time if it is to keep pace with a rate of advancement of knowledge peculiar to to-day, but quite undreamed of fifty years ago. The original writing of Kinnier Wilson's text was indeed overtaken even in his lifetime, and his lamented and premature death prevented him finally from covering his subject: thus, speech disturbances, in which he had always been interested, had not yet been dealt with by him when he last laid down his pen.

Thus, the original two-volume text, when it appeared in 1940 was, as it were, only a torso, though one of classic merit. It revealed the clinical neurology of the author's generation at its best, and the reader when he studied its pages met what is rare in medical writings, not merely an author but a man. For its pages were illumined by the writer's ripe experience and clinical insight, and by an artistry in the assessment of clinically observed states that the increasing number of technical demands upon the neurologist of to-day does not allow him the opportunity of acquiring. It is needless, perhaps, to add that Kinnier Wilson could write living English with an ease not vouchsafed to all medical authors.

It is because of all this that one must question the wisdom of the attempt to complete a

to bring up to date what is essentially a period piece, as is Gowers' still more famous text. It is not possible effectively to modernize a text, which was slowly put together during the twenties and thirties of this century, simply by the addition of what is new. Much that the original contained is now dated and obsolete, and only a drastic recasting of the entire work could really make of it a true picture of clinical neurology to-day. In short, the editors, with whose dilemma one must sympathize, have done either too much or too little, and admirers of the original text will surely regret the ineffective "new look" which has been imparted to a classic of the British school of neurology.

Many examples might be given of the split personality the book now has. Thus, "rheumatism and cold" still figure as significant causes of ocular nerve palsies, but there is no account of the important syndromes of unruptured intracranial aneurysm in which these nerves are so constantly involved. Amongst the remedies for polyneuritis, we still find sedative galvanism and sparks from a static machine. The patient with cerebral hæmorrhage still has croton oil and butter placed on the back of his tongue, as a measure less disturbing than an enema. Ocular muscle dystrophy still finds a habitation and a name with the variants of motor neurone disease, and so on.

Unless the new edition can be accepted as a faithful mirror of current knowledge and practice, its attempted rejuvenation can do it nothing but harm.

Nevertheless, the best of Kinnier Wilson—and what a best!—is still to be found amongst the pages of the three volumes to which—by reason of its accretions—the work has now grown, and the reader will find the added attraction of a chapter on aphasia, apraxia and agnosia from the accomplished pen of Sir Russell Brain, and an adequate subject index. The author bibliography, like the text, still hovers between the old and the new. It remains to be said that the production of the work is excellent.

Vitamins in Nutrition and Health. By Audrey Z. Baker, B.Sc., M.R.C.S., L.R.C.P. (Pp. xii + 148. 12s. 6d.) London: Staples Printers Ltd. 1954.

The author had studied under the late Sir Jack Drummond, F.R.S., and this book is dedicated to his memory.

She has given a very readable account of our present knowledge of the vitamins. Starting with a short historical note on each of them we are given a very brief account of the structural formula, where such is known, and on their use. In the second part of the book the source of the various vitamins is described, and both in the text and in tables there is set out in clear fashion an account of the different vitamins in common articles of food and in made-up dishes. Furthermore, instructions are given to those interested in cookery as how best to preserve the vitamin contents of food.

This up-to-date account of an important subject gives an accurate summary of the present state of our knowledge and is presented in a very readable form. It should prove useful to students and practitioners alike—and also to those who are concerned with the preparation of food in its relation to the health of the individual.

Clinical Bacteriology. By E. Joan Stokes, M.B., B.S., M.R.C.P., M.R.C.S. (Pp. vii + 288; 25 illustrations. 20s.) London: Edward Arnold (Publishers) Ltd. 1955.

This book fits admirably into the gap in bacteriological literature that lies between the larger and mainly theoretical monographs on the one hand and the manuals dealing solely with practical techniques on the other. It is primarily directed to helping the clinician and clinical pathologist to select from the many now available, the particular form of laboratory bacteriological examination most suited to their immediate needs, to employ the best available modern methods for this purpose and to interpret usefully, yet cautiously, the results that are obtained.

Amongst its ten chapters, the book deals with general laboratory procedures, records and reports, the various techniques applicable to specimens obtained from sites that are ordinarily sterile and from those possessing a normal indigenous flora, the identification of the bacteria recovered, the special problems presented by tuberculosis and the fungus infections, the antibacterial drugs and the errors that may result from lack of care in their use, immunological tests in clinical diagnosis, hospital epidemiology and the common nosocomial infections, and lastly with the preparation of media and apparatus. All these matters are presented with a modern emphasis and with directions that are ample, clear and accurate.

Dr. Joan Stokes has accomplished very successfully the task which she set herself. There can be few experienced clinical pathologists who would not benefit from the reading of this book while to the younger people entering this specialty it should prove invaluable both for reading and reference.

Practical Obstetric Problems. By Ian Donald, M.B.E., M.D., B.S., B.A., M.R.C.S., L.R.C.P., M.R.C.O.G. (Pp. xii + 578. 45s.) London: Lloyd-Luke (Medical Books) Ltd. 1955.

This book is the work of a keen and thoughtful teacher whose enthusiasm lends a vigour to his writing.

The book really consists of a series of essays some of them illustrated with figures. These figures have not been compiled into a series for this particular book but have been numbered in the sequence they appear in each particular chapter: thus figure 1 appears more than twenty times and the various figures 1 are distinguished by a prefix bearing the number of the chapter in which they appear.

Generally speaking the book is easy and enjoyable to read, the style being almost conversational, as, for example, one might quote a remark concerning the induction of labour for toxæmia in the case of an elderly primigravida. On this matter it is remarked that "if the patient's condition is bad enough to warrant induction at this age, there is a strong possibility that it warrants Cæsarean section instead".

The fact that the book is easy to read must not be allowed to hide the fact that it contains an enormous amount of information packed into relatively few words. It is possible that the balance of emphasis might be criticized and there are some places where the excellence of the theoretical or chemical or biochemical details is tremendously informative but hardly seems to come within the title of Practical Obstetric Problems. On the other hand such practical things as the use of Kielland's forceps are most admirably described and the reviewer was pleased to find an adequate description of what he considers to be a very useful instrument in a British obstetric textbook.

The greater part of the book is from the pen of the author whose name appears on the cover but others have contributed an occasional chapter, for instance, the chapter on toxæmia of pregnancy, those on breech presentation and on face and brow presentation, &c. Also the chapter on the relief of pain in obstetrics and the use and misuse of antibiotics.

The type is easy to read and most of the illustrations are very clear but one would hardly expect to see in a book that is not very richly illustrated and which is entitled Practical Obstetric Problems, a full-page illustration of a Servo-respirator and another of placental localization by radio-isotope method.

The few criticisms that have been offered are all of minor details and one can conclude that the book is well worthy of careful perusal and contains a great deal of instructive material.

Mr. Guy's Hospital. By H. C. Cameron, M.A., M.D., F.R.C.P. (Pp. xiv + 520. 30s.) London, New York, Toronto: Longmans, Green & Company. 1954.

The author has given us a history of Guy's Hospital which is indeed worthy of the Hospital itself. The task of writing a history of one of the big London Teaching Hospitals has been a labour of love to Dr. Hector Cameron, whose insight and analytical methods in the treatment of diseases in children have been used to produce a first-class account of Guy's. The book is well illustrated by coloured photographs and black-and-white reproductions of parts of the Hospital some of which are no more—having been destroyed in the blitz on the Borough during the Second World War.

To those of us who are Guy's men and women is also given a very human picture of the Medical and Nursing Staff of Guy's right up to the present day. The vivid pictures of the personalities who have helped to make the Hospital and Medical School are well portrayed, and a fair-minded and accurate account is given of the part which each of them has played in building up this great Institution.

In these changing times, when the Voluntary Hospitals are no more, it is good that we should be presented with an account of what the voluntary spirit in the Hospital field has accomplished in times gone by. This book will appeal not only to past and present generations of Guy's men but also to the historian.

Pediatric Diagnosis. By Morris Green, M.D., and Julius B. Richmond, M.D. (Pp. xv + 436; 8 illustrations. 50s.) Philadelphia and London: W. B. Saunders Company. 1954.

This book deals with pædiatrics under headings which are used by the patients and parents themselves, rather than under names of diseases, and its aim is to increase clinical skill through careful history-taking and examination, with a clear appreciation of the interpretation of the values of symptomatology.

The book is divided into four sections and the references throughout are given in the body of the text. This innovation should be most successful, making as it does for greater ease in looking up a particular group of signs and symptoms peculiar to one organ or region of the body.

The first section deals with the taking of a pædiatric history and stresses the value of a

friendly relationship between physician and parent which will make this "a progressive and continuous process".

The second is concerned with physical examinations and is arranged under systems and regions. There is a useful introduction to this section emphasizing the importance of the physician's personal approach to children in gaining their co-operation. Examinations of all areas of the body are dealt with in considerable detail, for instance, under "examination of the skeletal system" a summary of the causes of limp is included, and under "examination of the abdomen" an ætiological classification is given for hepatomegaly.

The third section is devoted to the interpretation of signs and symptoms. Here it is possible to look up, for example, œdema, and to find a list and short discussion on factors contributing to œdema, together with several relevant references.

The last section is concerned with the supervision of health from prenatal considerations to the adolescent, and assesses the "uniquely favourable position" of the physician to provide this supervision.

The authors are fully aware of the increased attention which is now being given to disturbances in growth and development and, accordingly, include tables giving heights and weights from birth to 18 years in an appendix.

Here is a book full of information of interest to those dealing in pædiatrics, and perhaps of most use to senior students and house officers, and those just embarking on the medical care of children. This is not to say that as a book of reference it will not also serve the more senior members of the profession, perhaps in the preparation of lectures as well as in day to day pædiatric practice.

Treatment of Ear, Nose and Throat Conditions. A series of articles by various contributors, edited by W. Stirk Adams, M.B., Ch.B., F.R.C.S., and R. R. S. Strang, M.B., Ch.B., F.R.C.S., D.L.O. (Pp. 24; illustrated. 2s. 6d.) London. Reprinted from the *Nursing Mirror*. 1954.

This collection of articles can be strongly recommended to nurses as an aid to understanding what the E.N.T. surgeon is trying to do and why he is trying to do it.

They are well illustrated and interesting but the emphasis of some articles is misleading. For example, if a patient has earache the important thing is to determine whether the patient has acute otitis media or not. In the article on earache acute suppurative otitis media has less space than otitic barotrauma or herpes oticus.

An illustration in the article entitled "Foreign Bodies" shows mercury bougies and Souttar's tubes which have nothing to do with the subject.

Another criticism is that the tray setting for changing a tracheotomy tube shows a suction tube which will barely pass through the tracheotomy tube. This sort of thing is misleading for nurses and should be rigorously avoided in articles written for them.

Diseases of the Skin. By George Clinton Andrews, M.D., F.A.C.P. 4th edition. (Pp. xi + 877; 777 illustrations. 65s.) Philadelphia and London: W. B. Saunders Company. 1954.

Increasing awareness of their ignorance about skin diseases leads more and more doctors to ask what textbook they should read on this subject. That such a question should even be asked seems to a perhaps biased reviewer a healthy sign. The student of medicine, whatever some may think, is no fool and he has a deliberately blind eye for skin diseases because he knows that his examiners will only rarely—and then unfairly—ask him questions about them. When the student qualifies and finds the dermatological 15% of his practice exposing him to a confession made sometimes boastfully, sometimes regretfully, of his ignorance of skin diseases then he may seek a book. This is the book he seeks; and indeed it would do his examiners no harm to read it also. The beginner in dermatology also might well digest this book for his first skin meal. Nine hundred pages and many rarities are a bit much for the undergraduate although he will find it a good reference book.

The arrangement of the book follows a fairly routine pattern; short introductory chapters on anatomy, pathology, general diagnosis and ray therapy (a clearly written section this) are followed by a chapter on dermatoses due to physical causes and another on pruritus and cutaneous neuroses. These are the weakest chapters, as if the author wanted to get quit of several isolated and several muddling conditions as quickly as possible. Few in this country would agree that "the most common causes of pruritus of the genitalia, groins and anus are moniliasis or tinea cruris, diabetes mellitus, seborrhœic dermatitis, psoriasis, and in women also *Trichomonas vaginalis*". The cutaneous neuroses are passed over with scant reference, for or against, to the views of the psychiatrists. Although we know that one school of psychiatry differs from another as much as chalk from cheese, however confused are the issues some expression of opinion on this vexed subject is called for in a book of

this size by so experienced an author. The following thirty chapters are essentially sound and interesting to any reader; it is difficult to discover anything which is not included. Of course, occasional criticisms can be made, as for instance against the section on ulcers of the legs in which a very complex problem is oversimplified. But in general the subjects are covered with admirable clarity, with sound judgment and surprising completeness. At the end of each chapter selected references are given for those whose appetite leads them farther. There are very many photographs, mostly good. The snare of expensive and not always very accurate colour pictures has been avoided. The paper and binding are up to accepted American standards. In the words of the historian it can be said of this book that it is a good thing.

The Vitamins: Chemistry, Physiology, Pathology. Edited by W. H. Sebrell, Jr., and Robert S. Harris (3 vols.; illustrated. Vol. 1 : §16.50; Vol. 2 : §16.50; Vol. 3 : §15.00) New York: Academic Press Inc., Publishers. 1954.

This is the most comprehensive account that has yet appeared, within one single work, of many of the aspects of vitamin science. Those aspects that are, purposely, not dealt with so exhaustively here are the clinical and the analytical, and, for these, other large treatises are already available. Certainly, in the fields of vitamin physiology and biochemistry, "Sebrell and Harris" is bound, for some years to come, to be one of the standard sources of reference for research workers. Each vitamin is dealt with in turn, systematically and intensively, under a series of a dozen or so different sections and subsections, each contributed by a separate author. As is inevitable in an enterprise of this kind, the contributions vary appreciably in merit, style of treatment, and literary quality. Most of the contributors are American, and to some extent this fact is reflected in the choice of bibliographical references in several of the articles.

It is perhaps too much to expect the ordinary scientific investigator to be able to afford the very high cost of these three volumes, for his own bookshelf; but they will be needed in the libraries of all institutes whose members specialize in the study of vitaminology.

Current Therapy 1954. Edited by Howard F. Conn. (Pp. xxxii + 898. 55s.) Philadelphia and London: W. B. Saunders Company. 1954.

Dr. Conn has attempted a herculean task in producing this volume of modern therapy relating to all branches of medical disease, including obstetrical and gynæcological conditions. (Modern surgical practice is not included.) He has enlisted the help of nearly four hundred contributors: and in relation to each of the medical diseases discussed has given first a short account of the principles of treatment, followed by a carefully documented account of the details of the various measures which are available. A balanced account is given of the place in treatment of any drug which may be useful.

Having discussed in detail the principles of treatment, an account is given of the method used for the treatment of each individual disease by an acknowledged authority. It is not a book that anyone can read from cover to cover: but is a book of reference which is a veritable mine of information presented and produced so as to make it invaluable to all who are interested in medical treatment.

Seventy-five Years of Medical Progress. 1878–1953. Edited by Louis H. Bauer, M.D., F.A.C.P. (Pp. 286. 30s.) London: Henry Kimpton. 1954.

The author has attempted a difficult task. With the help of twenty-six contributors in Canada and the U.S.A. he has collected an account of the progress made in twenty different medical subjects—including such subjects as General Practice, Neurological Surgery, Plastic Surgery, Psychiatry, Internal Medicine, and General and Thoracic Surgery. A historical account of medical progress early in the nineteenth century makes interesting reading: and we should be grateful to each contributor, as well as to the Editor, for the way in which the progress made by each of these branches of Medicine is presented to us. There is a tendency for all of us to take for granted the modern practice of Medicine in its many different branches, little realizing the painstaking stages of the work which has brought us to our present-day state of knowledge. It is good that we should pause and contemplate these various subjects for, as Professor Blalock says in his summary of the progress made in surgery: "Over the past seventy-five years the art of surgery has progressed far. How far it will go in the next seventy-five years lies in the realm of interesting speculation."

Section of Experimental Medicine and Therapeutics

President—Professor CLIFFORD WILSON, D.M., F.R.C.P.

[*February* 8, 1955]

DISCUSSION ON HEPATIC COMA

Dr. Sheila Sherlock (Postgraduate Medical School of London):

Portal Systemic Encephalopathy in Liver Disease

Patients with liver disease of many different types may show a characteristic neurological sequence, which, if persistent, culminates in coma—commonly called hepatic coma. The recognition of this syndrome is important, for it is frequently reversible and its occurrence can be anticipated and prevented. During the last eighteen months at the Postgraduate Medical School, we have seen 42 patients presenting this syndrome. The diagnoses were:

Acute virus hepatitis 9, portal cirrhosis 27, biliary cirrhosis 2, occlusion of the hepatic veins 1, centrilobular hepatic necrosis 2, and malignant liver, obstructive jaundice 1 patient.

The commonest causes are therefore portal cirrhosis and acute virus hepatitis.

The cerebral disturbance is a diffuse one and careful examination reveals involvement of almost all parts of the brain.

The *mental changes* resemble those other organic dementias. The onset is insidious and often difficult to recognize when the observer has no previous knowledge of the patient. The patient may become drowsy or excited, paranoid or manic. Bizarre behaviour is shown by such incidents as vomiting in the bedroom shoes or mixing rice pudding with meat. A clergyman under our care would become truculent and defæcate in the bath. Disorientation in time and space and other signs of confusion are followed by apathy, stupor and eventually coma resembling a deep sleep. The initial mental symptoms may be so severe that the patient is admitted to a psychiatric hospital, the underlying liver disease not being recognized.

The *motor disturbance* is characteristically shown by the flapping tremor reminiscent of the beating of a bird's wings. When the patient holds his arms in front of him with the fingers separated, rapid irregular movements occur in bursts, with flexion extension of the wrists and metacarpo-phalangeal joints. There is also a fine 6–9 per second tremor of the outstretched hands. The movements disappear in repose and are liable to be overlooked if the patient is only observed at rest and not asked to hold his hands in front of him. The tremor may be only transient, especially when the syndrome is associated with acute virus hepatitis. Rigidity of cogwheel type may be elicited. The tendon reflexes are exaggerated and there may be ankle clonus. The plantar responses are flexor. When coma is deep, the tendon reflexes may be diminished and the plantar responses extensor. Other neurological signs include mask-like facies, visual disturbances, ataxia, dysarthria and excessive salivation.

The *electroencephalographic changes* are well described by Foley *et al.* (1950) and reflect the diffuse cerebral change. There are bursts of bilaterally synchronous, symmetrical and high voltage two per second slow waves in the delta range. These are imposed on a normal alpha rhythm. These changes are occasionally found with other metabolic abnormalities of the brain, and are not entirely specific for hepatic coma. If the patient recovers, the EEG returns to normal.

Acute hepatic failure with virus hepatitis.—99·8% of patients with virus hepatitis recover uneventfully. The unfortunate complication of severe liver cell necrosis is therefore rare and correspondingly difficult to recognize.

In the jaundiced patient mental disturbance provides the earliest warning of the grave turn of events. The patient becomes disorientated, confused and rambling. Fœtor hepaticus and the "flapping tremor" are present. Jaundice is deep and persistent vomiting is a bad sign. The temperature rises. Daily percussion of hepatic dullness reveals shrinking of the liver under the right costal margin. If the illness is of longer than two to three weeks' duration ascites may be present.

Acute hepatic failure can also occur early in the course of virus hepatitis and is then extremely difficult to diagnose for jaundice is inconspicuous or absent. The predominant clinical features are mental and the patient may be admitted to a mental hospital without the hepatic disease being recognized.

Helpful diagnostic points are a history of epidemic jaundice in the community or recent injection therapy giving the opportunity for transmission of the hepatitis virus. There is anorexia, the liver edge is tender and percussion over the right lower ribs posteriorly causes

sickening, right upper quadrant, abdominal pain. The urine contains bilirubin but sensitive tests may be needed to demonstrate it. Fouchet's method and the new tablet test (Tallack and Sherlock, 1954) are equally satisfactory.

Acute hepatic failure in portal cirrhosis.—When hepatic failure complicates chronic portal cirrhosis an effort must be made to determine any factor which has depressed liver function. Gastro-intestinal hæmorrhage may have occurred from œsophageal varices and evidence of hæmorrhage must be sought. The bleeding is often slow and occult and melæna may be detected only by rectal examination. Acute infections such as pneumonia, minor surgical operations such as paracentesis abdominis and acute alcoholism are other possible precipitants.

When mental or neurological changes complicate well-documented cases of portal cirrhosis, the problem of recognition of the syndrome should not be difficult. Variable confusion, flapping tremor of the hands or arms, fœtor hepaticus, or stupor can be detected by careful examination. Indeed, if the portal cirrhosis is well recognized, it is difficult to know what else could cause this strange, neurological picture. Difficulty in diagnosis lies, rather, when cirrhosis has not been considered as the underlying cause and the patient is believed to be suffering from one of the other organic dementias. A history of alcoholism or previous jaundice should be sought, and clinical features of cirrhosis should be noted such as mild jaundice, spider nævi on the skin, palmar erythema, ascites, distended abdominal wall veins and enlargement of liver and spleen.

Rarely, the neurological changes in the cirrhotic patient are chronic and episodes of tremor, confusion, stupor and coma may occur for years before the correct diagnosis is made. This concept of "chronic intermittent hepatic coma" has only recently been recognized. In the intervals between the episodes, the patient may be almost normal. Deterioration can often be related to increased amounts of nitrogen-containing substances in the intestines.

Pathogenesis.—The essentially reversible change of this cerebral disturbance and its diffuse nature suggest that it is of metabolic origin and we shall discuss the possible toxic substances involved and the route by which they reach the brain. The syndrome can be induced by administering certain nitrogenous substances to a small proportion of patients with cirrhosis of the liver. These substances include a high protein diet, ammonium chloride, urea, methionine, or choline. This suggests that the toxic substance is nitrogenous. The relationship to ammonia intoxication will be considered by later speakers but my own view is that, at the present time, there is not sufficient evidence to assume that ammonia toxicity is the cause of the neurological changes.

The toxic nitrogenous substance or substances can, however, be shown to be of intestinal origin. Observations using oral ammonium chloride as the test nitrogenous substance and the hepatic vein catheterization technique have shown two routes by which toxic substances of intestinal origin might reach the systemic circulation in patients with liver disease. In patients with severe hepatocellular disease (e.g. severe virus hepatitis) the failing liver allows the substances to pass unaltered into the peripheral blood. In patients with cirrhosis, in addition to impaired liver function, the presence of a collateral circulation delivers portal vein blood directly to the peripheral blood stream before it can be metabolized by the liver. The neurological syndrome can therefore be termed a *portal systemic encephalopathy* (Sherlock *et al.*, 1954; White *et al.*, 1955). When the liver is normal, I have not seen the syndrome develop even with very gross portal systemic shunting of blood (e.g. congenital portal venous obstruction). Its development in a patient with cirrhosis depends on a balance between the extent of the collateral circulation and the capacity of the liver to metabolize toxic factors.

Fœtor hepaticus is often associated with the neurological syndrome and is probably also portal systemic in origin. The causative substance passes from the intestine into the systemic system by the same routes as I have outlined. The chronic low-grade pyrexia of cirrhosis may be of similar ætiology.

Treatment.—These observations offer practical guidance in the treatment of the neurological complications of liver disease and of hepatic coma which is one of them (Table I). Any possible depressant of liver function such as infection or hæmorrhage is treated. Dietary protein and any nitrogen-containing drugs are withdrawn and calories maintained

TABLE I.—TREATMENT HEPATIC COMA

ELIMINATE TOXIC NITROGENOUS SUBSTANCES	IMPROVE LIVER FUNCTION
Stop Protein, Methionine, Choline, Ammonium chloride	High Carbohydrate Diet By mouth
Give enemata and purgation	Intragastric drip 2 litres 20% glucose
Aureomycin 0·5 gram six-hourly by mouth	Intravenous drip 2 litres 20% glucose 1 litre 40% glucose
	Treat anæmia and infection

with a high carbohydrate diet. The bowels are emptied by enemata and purgation. As bacterial action on intestinal protein may be responsible for the toxic substances Aureomycin is also exhibited. As the patient recovers, dietary protein is increased up to the limit of tolerance.

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Mr. A. G. Riddell (Department of Surgery, University of Manchester):

Changes in Man and Animals with Portacaval Anastomoses

The first recorded instance of a neurological disorder, following the construction of a portacaval anastomosis, was the report by McDermott and Adams (1954). These authors described recurrent symptoms of confusion, stupor and coma in a patient, who had had a pancreatico-duodenectomy and portal-vein resection for carcinoma of the pancreas. The neurological disorder that followed this operation was clinically indistinguishable from hepatic coma. Attacks could be induced by the oral administration of a high protein diet, urea or ammonium chloride. At the onset of each episode, the concentration of ammonia in the peripheral blood was found to be greatly increased.

This syndrome of intolerance to a high protein diet in a patient with a portacaval shunt seemed analogous to the condition, which occurs in the Eck fistula dog, and is called "meat intoxication". Pavlov (Hahn *et al.*, 1893) first made the observation that some of his Eck fistula dogs when fed on meat, developed a peculiar neurological syndrome characterized by ataxia and blindness, and later followed by coma, and sometimes convulsions, before death. The cause of "meat intoxication" has remained obscure, although high blood ammonia levels have been reported by some investigators (Matthews, 1922; Monguió and Krause, 1934). A study was made of 19 attacks of "meat intoxication" both by forced feeding the Eck fistula dogs with meat and also in some instances by giving urea by mouth. It was found that when the symptoms developed the peripheral blood ammonia was raised to grossly abnormal levels. To determine whether ammonia was causally related to the onset of symptoms the following experiment was performed: The lowest blood ammonia level, which was associated with the onset of the symptoms of "meat intoxication", was determined in an Eck fistula dog. This level in one experiment was found to be 400 micrograms of ammonia-nitrogen per 100 ml. of whole blood. After an interval, when the dog had recovered, the blood ammonia level was raised to 400 micrograms by the intravenous injection of urease. The symptoms of "meat intoxication" were demonstrable approximately two hours after this blood level had been reached. This experiment, which was repeated on another animal, demonstrates that the symptoms are related to an abnormal concentration of ammonia in the blood (Riddell *et al.*, 1954). However, the method for the blood ammonia determination does not make it possible to distinguish between free ammonia and ammonia in loose chemical combination in the blood (Conway, 1950; McDermott and Adams, 1954).

Microscopical examination of the brains of the Eck fistula dogs, that had had "meat intoxication", showed the glial change, that was reported by Adams and Foley (1953) to occur in patients dying from hepatic coma, namely, hypertrophy and hyperplasia of the nuclei of the protoplasmic astrocytes.

Up to the time that McDermott and Adams (1954) described the occurrence of neurological symptoms following a portacaval shunt, no account of this condition of "episodic stupor" had been recorded in patients, who had shunts performed for the relief of portal hypertension. Such cases have now been reported (McDermott *et al.*, 1954; Sherlock *et al.*, 1954) and it is probable that 10% of patients who undergo shunt surgery for portal hypertension will develop one or more attacks of episodic stupor.

Observations on 9 patients, with cirrhosis of the liver, who developed hepatic coma after massive hæmorrhage from œsophageal varices showed that in these cases high blood ammonia levels occurred within several hours of the onset of the bleeding. During the ensuing forty-eight hours the blood ammonia level would fall to relatively normal levels, but the neurological state would change more slowly. This time-relationship between the blood ammonia level and the neurological state was similar to that seen in "meat intoxication" in the Eck fistula dog. Experiments on Eck fistula dogs have shown that the introduction of blood into the alimentary tract is followed by the occurrence of a great increase in the peripheral blood ammonia level, which is associated with onset of the signs of meat intoxication. It appears, therefore, that the presence of blood in the alimentary tract is the chief precipitating cause of hepatic coma following hæmorrhage from œsophageal varices. Such a mechanism has been previously suggested by Gaustad (1949).

The experiments on Eck fistula dogs and observations on patients with cirrhosis of the liver show that it is the deviation of the portal blood away from the liver which leads to the development of hepatic coma. It is suggested that ammonia either free in the blood or in chemical combination is a cause of the neurological symptoms observed in patients with naturally occurring systemoportal anastomoses or in patients with artificially constructed shunts.

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Dr. W. H. J. Summerskill (Department of Medicine, Postgraduate Medical School of London):

Blood Ammonium Levels in Liver Disease

It has been suggested by Dr. Sherlock that the syndrome of hepatic coma can be attributed to the toxic effect on the central nervous system of nitrogenous substances originating from the intestines. A high level of ammonium is present in portal vein blood coming from the intestines, and Mr. Riddell has related neurological complications following portacaval anastomosis to deranged ammonium metabolism.

The oral administration of certain nitrogenous substances to patients with cirrhosis may precipitate "impending hepatic coma" (Phillips *et al.*, 1952) and ammonium chloride is the simplest compound having this effect, although ammonium can be derived from the other exciting agents by bacterial action in the intestines. Moreover, high blood ammonium levels are commonly found during spontaneous episodes of hepatic coma (Traeger *et al.*, 1954).

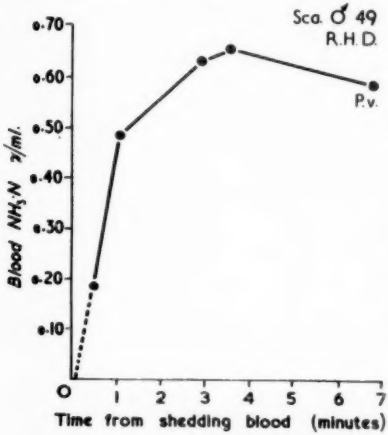

FIG. 1.—The curve of blood ammonium liberation in a normal subject (from *J. clin. Invest.*).

The theoretical basis for blood ammonium determination in liver disease is thus established and the investigations which will be reported were carried out with the help of Dr. E. A. Phear and Dr. L. P. White on the group of patients already described by Dr. Sherlock.

The most accurate method available for blood ammonium estimation is the microdiffusion technique of Conway (1950), but it has the disadvantage of uncertain specificity because the immediate liberation of ammonium from substances in shed blood cannot be prevented. By carrying out rapid, timed, serial estimations on each blood sample, a curve of ammonium liberation can be constructed (Fig. 1) and from this we have selected three-minute values, as most of the rapidly liberated ammonium is evolved by this time and reliable comparative data is thus obtained. Zero-time values, derived by extrapolation, may be more significant, but they depend on the accuracy of only two early readings.

In patients without liver disease, little ammonium is present in peripheral and hepatic vein blood, although relatively high values are found in portal vein blood (Fig. 2). This portal-hepatic vein difference reflects ammonium metabolism in the normal liver. The ammonium content of renal vein blood (mean value 1·4 μg./ml.) suggests that the kidneys may contribute to peripheral blood ammonium.

High blood ammonium levels were sometimes found in liver disease and were common in hepatic coma (Fig. 3). In patients with uncomplicated liver disease, mean values were not greatly elevated, but in those with neurological disorder very high mean levels were obtained. However, there was some overlap between the two groups and on two occasions hepatic coma was associated with a normal blood ammonium level.

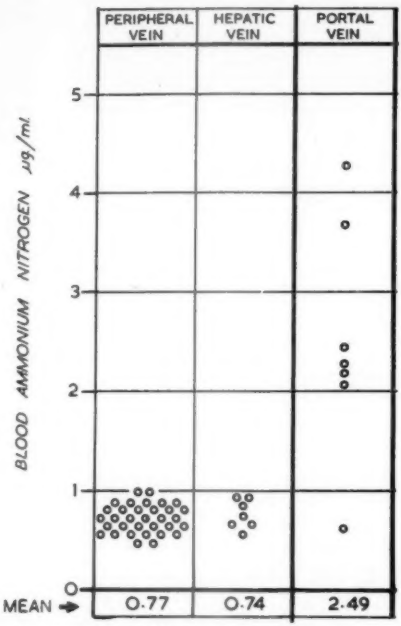

FIG. 2.—Normal blood ammonium levels at different sites.

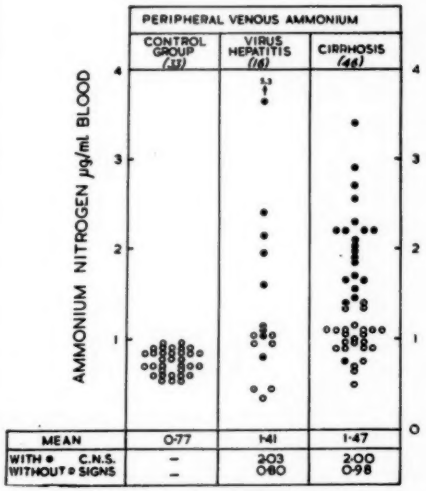

FIG. 3.—Peripheral vein ammonium levels in patients with liver disease and hepatic coma.

It appears likely, therefore, that disordered ammonium metabolism may allow ammonium to pass from the portal vein to the systemic venous circulation in some patients with liver disease. This can be demonstrated by taking simultaneous samples of blood from peripheral and hepatic veins following an oral dose of 3·0 grams ammonium chloride.

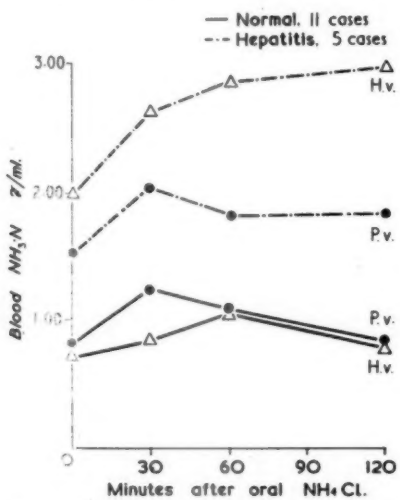

FIG. 4.—Ammonium tolerance in patients with acute hepatitis (from *J. clin. Invest.*).

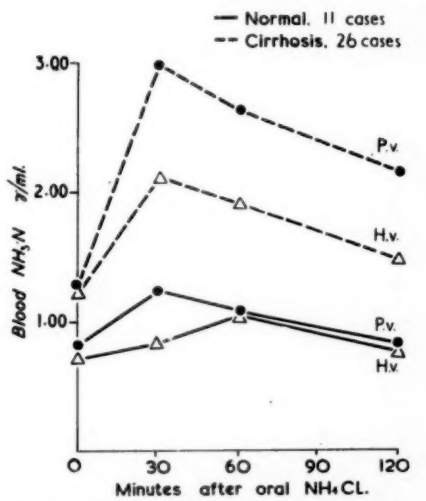

FIG. 5.—Ammonium tolerance in patients with cirrhosis (from *J. clin. Invest.*).

Figs. 4 and 5 are reproduced from White *et al.* (1955) by kind permission of the Editor-in-Chief of the *Journal of Clinical Investigation.*

Ammonium tolerance curves from patients with acute hepatitis and cirrhosis differ from those obtained from subjects without liver disease undergoing cardiac catheterization for cardio-respiratory investigations (Figs. 4 and 5). In patients with acute hepatitis, high fasting blood ammonium levels with an exaggerated and sustained rise in hepatic vein values were found. These changes were reflected at the periphery and showed that the diseased liver allowed ammonium from the portal vein to pass into the systemic venous circulation. In patients with cirrhosis, high fasting levels, exaggerated peaks and a delayed return to initial values occurred. Abnormal hepatic vein values showed the effect of impaired liver function, but the predominant abnormality was in peripheral vein levels and demonstrated the added influence of diversion of portal blood direct to the systemic circulation through collateral vessels.

These findings suggest that blood ammonium levels in liver disease depend on liver function and the portal systemic shunting of blood. Whether shunting of portal blood in the absence of impaired liver function can produce high blood ammonium levels is uncertain. We have seen five patients with good liver function in whom occlusion of the portal vein diverted the entire portal blood flow through collateral channels. Blood ammonium levels were normal in every patient, so we believe that some impairment of liver function is necessary before elevation of blood ammonium values occurs.

The relationship between blood ammonium levels and neurological status at the time of sampling is complex. The proportion of high values (above 2·0 μg./ml.) increases as neurological deterioration progresses, but 10% of values are normal at every stage. Repeated estimations in individual patients during the terminal week of hepatic coma showed wide fluctuations which were unrelated to the clinical state. Values were abnormal at some stage in every patient, but normal readings were not uncommon.

Rarely, the signs of hepatic coma occur in a chronic form associated with an extensive portal collateral circulation and only mild impairment of liver function (Sherlock *et al.*, 1954), and in these patients a correlation between neurological status, blood ammonium levels and the intake of nitrogenous substances can often be appreciated. Such patients have features similar to those described in some surgical cases by Mr. Riddell, but they represent only a restricted aspect of the problem of hepatic coma.

These results demonstrate that ammonium from the portal vein may reach the systemic venous circulation by passing through a diseased liver or through portal-systemic collateral channels. This explains the high levels of blood ammonium in hepatic coma, but the significance of ammonium intoxication as a causal factor remains speculative. The application of blood ammonium estimation to clinical problems is limited by the laborious nature of the procedure, which involves timed pipetting of aliquots at the bedside and the determination of "normal" values by each laboratory, and by the difficulty experienced in interpreting normal or equivocal results. Recognition of the clinical sequence remains the most reliable diagnostic method, although blood ammonium levels above twice the normal figure will support the diagnosis where doubt exists.

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Dr. W. T. Cooke:

Other Possible Nutritional Factors in the Production of Neurological Changes

It is evident that hepatic coma should be grouped with other metabolic comas being reversible and not necessarily fatal. It does not, however, correspond with others in that there is as yet no specific laboratory finding and diagnosis is dependent upon the clinical history and signs. But although the clinical picture varying between tremor, asterixis, confusion, coma together with certain EEG findings is highly suggestive of liver disease, similar clinical pictures have been noted in conditions in which there was no obvious liver damage, although it could probably be postulated that liver function was not normal. Foley and Adams (1953) noted the characteristic asterixis in 3 patients with polycythæmia and 3 with uræmia.

We have encountered this syndrome in varying degrees of severity in four different groups of patients: in none was there evidence that the liver was the primary cause of their illness, but this does not deny the possibility that all may have had some upset in the metabolic function of the liver and, strictly speaking, it might be argued that they are not cases of hepatic coma.

The only patient who had been seriously studied in the first group is a patient of Professor P. C. Cloake.

Case I.—A 70-year-old spinster, first seen four years ago on account of episodes of slurred speech and ataxia. Since this time, she has had a number of attacks lasting two to fourteen days, in one of which she was unrousable. In between these episodes she is able to lead a normal life and demonstrate that she has no intellectual deterioration though mild asterixis is always present. Investigations showed no abnormality in liver function test, liver biopsy, fat balance, blood count, pneumoencephalogram, angiogram, intestinal radiology, amino acid blood levels and amino acid excretion. Blood ammonia taken during the recovery phase of one episode was just above our normal level, but below those found in cirrhosis. EEG taken during the relatively normal phase, although still with asterixis present, is grossly abnormal with a predominance of theta waves 4–7 p./m.

In the second group are two patients in whom confusion, inco-ordination and asterixis took place in association with cyanosis and cor pulmonale.

Case II.—A patient of Professor W. M. Arnott, a man of 51, has been followed for twelve months on account of a number of severe confusional episodes, mild emphysema, mild compensatory polycythæmia and an expanding lesion of unknown nature in his lung. In his earlier episodes he had been regarded as demonstrating the type of coma associated with a high arterial CO_2. In between the episodes he has been well enough to return to work. On his last admission he was noted to be confused and to present the typical hepatic tremor affecting both the arms, legs and face. These tremors could be relieved by oxygen administration and increased when he was cyanosed. After ten days in hospital all the abnormal neurological features had disappeared. His liver function tests were completely normal. The diagnosis of the intra-pulmonary lesion is not yet clear, though it has been assumed to be a carcinoma.

Case III.—A patient of Dr. Paul Davison, a woman of 36, was admitted semi-comatose and cyanosed with right heart failure due probably to pulmonary hypertension. She demonstrated gross asterixis which disappeared completely after thirty-six hours in the oxygen tent and had not reappeared. She, in contrast to the previous case, was anæmic with Hb of 9 grams/100 ml. Her liver function tests were completely normal.

In the third group are 2 patients with severe malnutrition. A group in which fatty livers and the role of the liver in producing comas might play a primary part.

Case IV.—Man aged 30 who developed pancreatic atrophy and low serum proteins as a complication of partial gastrectomy and had a gradual downhill course over two years. During this period he had one episode of confusion of Wernicke's type associated with nystagmus and severe exacerbation of glossitis which was apparently related to the administration of antibiotics by mouth and methionine by vein. He also had two further episodes of mental confusion and increasing coma during which there was no evidence of electrolyte depletion. The first episode recovered spontaneously after seventy-two hours; the second proved fatal after forty-eight hours. Both were associated with a coarse tremor and with low blood sugars.

Case V.—Girl aged 18 with hypoproteinæmia, malnutrition and dehydration due to extensive regional enteritis, became semi-comatose following an exacerbation of her diarrhœa and general depletion of water and electrolytes. During the recovery phase choreiform movements affecting the legs, arms and face and slurred speech were present: full repletion of water and electrolytes led to the disappearance of the signs. During the next four months two further episodes of diarrhœa led to the reappearance of these features. She died three years later of pulmonary tuberculosis.

In the fourth group are 3 patients with the steatorrhœa syndrome with no significant malnutrition. All were severely troubled at times with diarrhœa. They underline the close intermingling of nutritional factors in producing their condition and the difficulty there can be in clearly delineating the boundaries, if boundaries there be, between the differing causes of coma, such as hepatic coma and Wernicke's. Their principal findings may be summarized:

Case VI.—Man aged 56. Idiopathic steatorrhœa. Had suffered intermittent diarrhœa for many years, a macrocytic anæmia for two years and episodes of mild mental confusion and unsteadiness of gait for six months. He presented tremor of hands—mild asterixis for some weeks before death in coma. There were no eye signs. Autopsy showed a normal liver, astrocytic hyperplasia and fibrosis around the 3rd and 4th ventricles together with some degenerative changes in the posterior columns.

Case VII.—Man aged 36. Whipple's disease. Well until two years prior to death when he had severe fatty diarrhœa and some mental confusion for six months. He relapsed five months prior to death. There were no neurological features except moderate coarse tremor and mild asterixis. He had periods of mental confusion. He died in coma of forty-eight hours' duration. Autopsy showed intestinal features of Whipple's disease, normal liver histology and cerebellar atrophy.

Case VIII.—Man aged 72. Whipple's disease. Patient had been unable to work for fifteen years owing to difficulty in walking. For four years he had had attacks of diarrhœa. He was admitted owing to an exacerbation of diarrhœa and the finding of a mass in rectum. This proved to be non-malignant. Following operation he was noted to be mentally apathetic and unable to concentrate though relatives stated that this state was little different to that before operation. He had signs in addition of posterior column and pyramidal tract lesions, moderate steatorrhœa and coarse tremor

of his hands. Four weeks after operation, he deteriorated, marked asterixis was present for twenty-four hours before he lapsed into coma. Autopsy showed normal liver histology and intestinal findings compatible with Whipple's disease. The findings in the C.N.S. are not yet available.

Neither EEG nor blood ammonias were done on these patients but EEGs have been obtained on other patients with steatorrhœa demonstrating diffuse abnormalities and the blood ammonia has been found to be raised in some patients with diarrhœa and steatorrhœa. In none of the 3 patients did hypokalæmia or hypoglycæmia appear to play a role. In none of our patients have we made any detailed study on magnesium metabolism. It will be recalled that Flink and his colleagues (1954) have described the occurrence of low serum magnesium in cirrhosis of the liver and have described the clinical manifestation of this deficiency as being gross muscular tremor, athetoid and choreiform movements, and in the severe forms convulsions. It must be concluded that the neurological features of the syndrome will be found in many conditions when looked for.

In searching for fresh leads to unravel the cause of these comas we are at present studying the urinary excretion of certain phenolic and acidic compounds, some of which may have toxic effects (Aterman *et al.*, 1953). Patients with cirrhosis and most of the patients with steatorrhœa excreted a large number of abnormal compounds of this type and that there is at least one compound—which as yet we have been unable to identify—consistently present in the severe cases, including the last 3 patients. I mention this work, not because I believe it is providing the answer to this metabolic upset, but because it illustrates the vast number of as yet unknown ways that metabolism can go wrong and produce these episodes of coma.

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Mr. G. Wooler: In the Department of Thoracic Surgery at Leeds we have seen 97 cases of portal hypertension. Until 1947 the patients submitted for surgery either had splenectomy performed or various operations to try to improve the collateral circulation between the portal and systemic venous systems. During 1947 we performed 6 portal systemic anastomoses (2 portacaval and 4 lieno-renal); 3 of these patients died in the post-operative period and we were not sure that the 3 which survived had in fact patent anastomoses.

On February 3, 1948, Allison first performed his "devascularization operation": since when 26 patients have had a similar type of operation. The object of this operation is to stop the blood getting into the veins lying in the submucosa of the œsophagus and stomach which become varicose and bleed. The large collateral vessels which course over the surface of the stomach and œsophagus to the subphrenic veins and the azygos system are left intact to carry the portal blood. The veins passing from these collaterals through the muscle of the stomach and œsophagus are all divided between ligatures. The operation may be performed in two stages, but eventually the œsophagus and stomach are freed of all vessels from the level of the aortic arch to the pylorus. This operation increases the portal blood pressure and so produces the opposite result to a portal systemic anastomosis.

Results of 26 "devascularizations":

(*a*) 4 post-operative deaths: 2 due to mesenteric thrombosis, 1 to gangrene of stomach, and 1 to hæmopericardium.

(*b*) 6 post-operative complications: 1 patient became drowsy, but recovered and is now well. 3 developed ascites and abdominal discomfort, and 2 others had melæna. These complications were considered to be due to thrombosis in the portal system, and they all recovered after a course of anticoagulants.

(*c*) 4 patients have had recurrence of bleeding one to four years after this operation.

During the past three years, 24 patients have had portacaval anastomoses performed (5 were end to side, and 19 side to side).

Results of 24 portacaval anastomoses:

(*a*) 4 post-operative deaths. 3 died in coma, and 1 of mesenteric thrombosis.

(*b*) Post-operative complications. 10 patients (other than (*a*)) became drowsy and showed signs of various stages of intoxication. 9 responded well to treatment and now have no symptoms. The other appears to have permanent mental damage, although this was present in a minor degree before the operation. One patient bled in the immediate post-operative period from an overdose of heparin.

(*c*) No recurrence of hæmorrhage.

The difference in the post-operative course of these two operations has been most striking. Portal systemic intoxication is rare after the devascularization operation but common after portacaval anastomosis. It usually occurs between the second and tenth post-operative days. It appears to be related to the shrinkage of the spleen and hæmolysis of the excess red cells which are poured into the circulation. This is the most critical period after the operation. Intoxication occurring later can be controlled by diet and treatment but not always in the post-operative period.

Last December I performed a portacaval anastomosis on a woman of 62 who was bleeding profusely at the time. The bleeding stopped immediately the clamps were removed and she remained well until the second day when she became drowsy and then passed into deep coma. She remained deeply comatose for another two days and her condition looked hopeless so I reopened her and placed a Blalock clamp across the anastomosis leaving the handle outside the abdomen. Within twelve hours of cutting down the blood flow she was completely conscious and remained so for another forty-eight hours. She then bled again and the clamp was opened. Six hours later she passed again into coma and eventually died.

Thus it appears that it is an advantage to be able to control the blood flow through a portacaval anastomosis during the critical days following the operation. I have designed a simple clamp which may be placed across the anastomosis and controlled by the handle outside the abdomen. It can be removed easily and I intend to use it on the bad risk cases, in the hope of preventing coma.

FIG. 1.

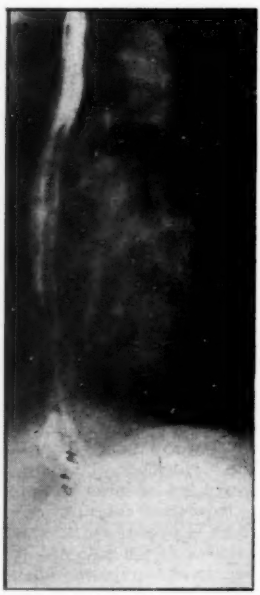

FIG. 2.

FIG. 3.

FIG. 1.—Barium swallow (Dr. Johnstone) showing the large vascular œsophagus distended with varices.

FIG. 2.—The same patient after a portacaval anastomosis had been performed. The œsophagus now appeared normal.

FIG. 3.—Showing shrinkage of the spleen on successive days after a portacaval anastomosis. The disappearance of the spleen indicates that the anastomosis is widely patent.

—4th day—tip just palpable C—3rd day B—2nd day A—1st day

Dr. Jonathan Gould: In the presentation of the clinical cases the syndrome referred to as neurotical could better be presented as a psychiatric illness. It has all the features characteristic of a toxi-organic psychosis, for even though coma in this latter condition is not present it occurs not infrequently in alcoholic psychoses. The precipitating factors mentioned by the first speaker are exactly comparable to those known to be precipitants in

delirium tremens. In the patient described cinematographically the jactitations were similar to those in delirium tremens as were the facies and I noticed that his tongue was raw. I was not able to see, however, whether he exhibited other signs of vitamin lack. He did not indeed have a true intention tremor for his finger quite accurately reached the end of his nose and trembled only thereafter.

Hepatic coma has been described by the previous speakers as occurring with and without evidence of liver damage or disease; with uncomplicated malnutrition and with steatorrhœa; it has not, however, been described earlier in this Discussion in association with alcoholism in any of its grosser forms although liver damage is common in alcoholism. The problem of nutritional factors other than the disturbed nitrogen metabolism in the causation of hepatic coma has been stressed.

The high levels of blood ammonia have been shown principally to be an indicator of the metabolic upset which it is agreed exists in hepatic coma but the significance of the ammonia in the mental disorder has been challenged and its estimation has been abandoned as it has been shown not to be relevant to the changes in the general clinical picture.

We have been presented with a clinical conjunction of disturbed mental function leading often to loss of consciousness and even death in association with variable degrees of disturbed liver function. The liver is the largest body storehouse of the B vitamins and it, as was shown by Peters (1938) in the experimentally depleted animal, is the first organ to pick up injected vitamin B_1. It is very closely followed in avidity in these experiments by the brain. The brain has a respiratory quotient of 1 and metabolizes essentially only glucose. For brain function and hence mental function to proceed normally this metabolism must remain unimpaired. For its adequate progress Barron (1939) has shown that a range of the B vitamins are necessary to the enzymatic architecture and the metabolic integrity of the brain cells. Sydenstricker (1943) showed that coma with curious neurological characteristics could ensue in a condition described as Acute Nicotinic Acid Deficiency Encephalopathy. The liver, too, has a parenchyma which must respire and it, too, has a high respiratory quotient. The brain indeed never lowers its respiratory quotient unless it is almost soaked in alcohol and then the patient is in coma. Quastel in 1939 and again in 1953 showed the relationship of the effects of barbiturate on the respiratory quotient of the brain and that these depressant effects were reversible by vitamin B_1. My own approach to the treatment of toxi-organic delirium due to alcohol and/or drugs was described in this Society in 1953, and elsewhere (1955). It involves the use of large quantities of vitamin C, the B group and glucose.

We have here discussed investigations aimed at finding a single product of deviated metabolism which acts as a toxin on the brain but I suggest that it is very desirable and most important to consider the protection of the metabolic integrity, the enzymatic architecture and hence the intracellular carbohydrate respiration of both the brain and liver tissue. As Barron has indicated the B group vitamins and glucose are essential to this.

In discussing the treatment of the patient going into coma after portacaval shunt I recall a case which I have published elsewhere (1953), who had been submitted to portacaval shunt and who had œsophageal varices. Forty-eight hours after operation he became acutely confused. At that time I took his confusion to be due to anæsthesia but the discussion this evening has shaken my opinion a little. However, this man was out of confusion, clear and rational within fifty minutes with the aid of large amounts of vitamins.

One of the functions of the liver is to convert ammonia to urea and this carboxylation process involves hydrogen transfer which is one of the functions of the B group vitamins in enzymatic form. The clinical conditions of the patients in which hepatic coma occurs suggest that there is, with chronically or acutely impaired health, slow or sudden depletion of the body stores of the vitamin B group. It is conceivable that, in the conditions presented therefore the liver cell metabolism fails but at the same time intracellular brain carbohydrate metabolism, also depleted of its B-containing-enzymes, breaks down. Once this occurs a toxi-organic psychosis ensues.

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